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## Efficacy of transdermal methotrexate iontophoresis and low dose oral methotrexate in the treatment of palmoplantar psoriasis

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### Abstract

**Background:** Psoriasis exclusively involving the palms and soles is known as palmoplantar psoriasis. Though it involves a small body surface area, poses significant morbidity in daily activities of patients. Systemic treatments are indicated for extensive and refractory cases. Systemic toxicity limits the usage of systemic drugs. Methotrexate a time proven drug for psoriasis has been used in oral, injectables and topical formulation. Iontophoresis is a transdermal drug delivery system which can enhance the penetration of methotrexate drug locally, minimizing the systemic side effects.

**Aim:** To evaluate the efficacy of transdermal delivery of methotrexate through iontophoresis in comparison to oral methotrexate in palmoplantar psoriasis.

**Methods:** Forty patients attending the psoriasis clinic with psoriasis involving palms and/or soles are randomly allocated into two groups (20 in each). Methotrexate iontophoresis group was treated with iontophoresis weekly once for 16 weeks whereas oral methotrexate group was given 0.2-0.4mg/kg/week every weekly for 16 weeks. The severity of palmoplantar psoriasis was assessed by mPPPASI at baseline, 4,8,12 and 16 weeks.

**Results:** Males are higher in both study groups. The most common age group of onset was at 40-60 years. Palms and soles was involved in 55%, soles only in 27.5% and palms alone in 17.5%. Mean mPPPASI reduction was gradual in both groups with comparable efficacy. mPPPASI reduction at 16 weeks was higher in Oral methotrexate with good compliance.

**Conclusion:** Methotrexate delivered by Iontophoresis was equally effective as Oral methotrexate in treatment of palmoplantar psoriasis.

**Keywords:** Transdermal, methotrexate, Palmoplantar, Ppsoriasis

### Introduction

Psoriasis is a chronic inflammatory immune mediated proliferative skin disorder that predominantly involve the skin, nails, and joints [1]. It has strong genetic predisposition and autoimmune pathogenic traits [2]. It ranges in severity from a few scattered red, scaly plaques to involvement of almost the entire body surface. It may progressively worsen with age, or wax and wane in its severity: the degree of severity depends on inheritance and environmental factors [3]. Palmoplantar psoriasis is a variant form of psoriasis that characteristically affects the skin of the palms and soles and comprises 3-4% of all cases of psoriasis. It can present with various morphologies ranging from sharply demarcated hyperkeratotic plaques to predominantly pustular lesions, or a combination of the two. Though affecting a small percentage of a patient's body surface area, palmoplantar psoriasis can cause significant discomfort and physical disability, particularly when painful deep fissuring or bleeding occurs [4].

Methotrexate is a time-tested drug commonly used in all clinical types of psoriasis. It is very effective in treating mild to severe extensive cases of psoriasis vulgaris as well as psoriatic arthritis and pustular psoriasis. However, as a monotherapy on higher doses for prolonged period of time it can cause serious haematological and hepatic side effects. To avoid systemic toxicity, methotrexate can be delivered to the localized areas of palms and soles using advanced formulation of drug delivery system like iontophoresis. Iontophoresis is a transdermal drug delivery system which can enhance methotrexate absorption and efficacy without any systemic side effects [5]. We conducted this study to evaluate the efficacy of

methotrexate administered by iontophoresis in comparison to oral methotrexate in palmoplantar psoriasis

**Materials and Methods**

This prospective interventional was conducted in patients attending the psoriasis clinic in the department of dermatology for a duration of 2 years. A total number of 235 psoriasis patients screened of which 54 patients had localized palmoplantar psoriasis were enrolled in the study. 14 patients did not come for regular follow up and were withdrawn from the study. The study group consisted of forty patients and were randomly allocated to methotrexate iontophoresis group and oral methotrexate group. Ethical clearance was obtained from the institutional ethical committee. Informed consent was obtained from all patients after clearly explaining about the study methods and side effects.

**Inclusion Criteria**

Patients above 14 years of age with psoriasis involving the palms and/or soles who had not undergone any treatment in the past 3 months and willing for follow up were included in the study.

**Exclusion Criteria**

Patients who had infected fissured psoriatic plaque, topical and systemic corticosteroids, immunosuppressive therapy, pregnancy, breastfeeding, hepatic illness, renal disease, sensitivity to methotrexate and below 14 years of age were excluded from the study.

Baseline hematological investigation were done in all patients before starting the therapy and at the end of the

study period.

**Methotrexate Iontophoresis Group**

Twenty patients were randomly allocated to the group. Injection Methotrexate (Folitrax, manufacturer: Ipca) 50mg/2ml was diluted in 50ml of sterile water to obtain a concentration of 1mg/ml. The methotrexate solution was soaked in a sterile gauze and placed over the psoriatic lesions of palms and soles. The gauze was covered by an aluminum foil and the hands/feet are placed on the electrode of iontophoresis machine submerged in the water. The direct current was passed through the electrode and the patient experience mild tingling and numbness. The current strength was maintained at 5-10mA for 15-20 minutes depending upon the patient tolerability. The procedure was repeated every weekly over a period of 16 weeks and the modified palmoplantar psoriasis area severity index (m-PPASI) was calculated at baseline, 0,4,8,12,16 weeks and analyzed.

**Oral Methotrexate Group**

Twenty patients were randomly allocated to the group, oral methotrexate tablet (folitrax, manufacturer: Ipca) was given at initial test dose of 2.5 mg for one week. After ruling out hematological abnormalities at first week, 0.2-0.4mg/week dose of oral methotrexate tablet was given weekly for 16 weeks. All patients were assessed using m-PPASI periodically at baseline (0 visit) and every four weeks till 16 weeks.

**Calculation OF m-PPASI**

Clinical severity	Right palm	Left palm	Right sole	Left sole
1.Erythema(E)	0-4	0-4	0-4	0-4
2. Induration(I)	0-4	0-4	0-4	0-4
3.Desquamation (D)	0-4	0-4	0-4	0-4
Extent of involvement(e)	0-6	0-6	0-6	0-6
Total extent	0.2xe	0.2xe	0.3xe	0.3xe
Max score =total extent × clinical score	A=(E+I+D)0.2xe	B=(E+I+D)0.2xe	C=(E+I+D)0.3xe	A=(E+I+D)0.3xe
Total m-PPASI= A+B+C+D				

Clinical severity: 0- no involvement, 1-mild, 2-moderate, 3-severe, 4-very severe

Extent of involvement: 0 -none, <10% -1, 10-29% -2, 30-49%-3, 50-69%-4, 70-89%-5, 90-100% -6.

Total m-PPASI score range from 0 to 72.

**Results**

The results were discussed under age, sex distribution, site of involvement and m-PPASI reduction.

**Age:** In our study of palmoplantar psoriasis majority were in

the age group of 40-60 years (52.5%). The youngest patient presented with palmoplantar psoriasis was 20 years and eldest was 70 years. The mean age in the study was 46.3 years.

**Table 1:** Age distribution

Group	Males	Females	Mean age
Methotrexate iontophoresis	12	8	45.8
Oral methotrexate	11	9	46.8
Total	23	17	46.3

**Sex**

Males were more common in our study group comprising 23(57.5%) cases and females 17(42.5%) cases. Iontophoresis group had 12 males and 8 females. Oral methotrexate group had 11 males and 9 females.

**Sites Involved**

In the present study both the palms and soles were involved in 21(52.5%) cases followed by soles with 11(27.5%) cases and the palmar alone involvement with 7(17.5%) cases. In

Iontophoresis methotrexate group, the sites involved were both palms and soles in 9 (45%) cases, only soles in 7 (35%) cases and only palms in 4 (20%) cases. In Oral methotrexate group, the sites involved were both palms and soles in 13(65%) cases, only soles in 4 (20%) cases and only palms in 3(15%) cases.

**m-Pppasi Reduction**

The mean m-PPASI reduction showed a gradual decrease at every month in both groups. (Table-2) The reduction in

m-PPASI was higher in Oral methotrexate group with 31.23 at baseline and 0.47 at 16 weeks compared to iontophoresis methotrexate with 28.04 at baseline and 1.07 at 16 weeks. The oral methotrexate group showed significant percentage of reduction in m-PPASI with

47.67%, 72.91%, 88.12%, 98.49% at 4,8,12 16 weeks respectively compared to iontophoresis group with reduction of 38.69%, 61.44%, 84.55%, 96.18% at 4,8,12,16 weeks respectively. (Table-3)

**Table 2:** Mean reduction in m-PPASI in two groups

Duration	Mean m-PPASI	
	Methotrexate iontophoresis	Oral methotrexate
Baseline	28.04	31.23
4 Weeks	17.19	16.34
8 Weeks	10.81	8.46
12 Weeks	4.33	3.71
16 Weeks	1.07	0.47

**Table 3:** Mean percentage reduction in m-PPASI in two groups

Duration	Methotrexate iontophoresis	Oral methotrexate
Baseline	0%	0%
4 Weeks	38.69%	47.67%
8 Weeks	61.44%	72.91%
12 Weeks	84.55%	88.12%
16 Weeks	96.18%	98.49%

**Response to therapy**

Based on percentage reduction in mPPASI score the results were graded as excellent (100%), good (75-100%), moderate (50- 75%) and poor (<50%).

In Iontophoresis group out of 20 patients 14 patients had complete clearance at 16 weeks and 4 had good response 2 patients had poor response.

Therefore, in Iontophoresis group 70% of patients had excellent response and 20% of patients had good response and 10% of patients had poor response at 16 weeks.

**Response to therapy in iontophoresis group**

**Table 4:** Response to treatment in palmoplantar psoriasis in methotrexate iontophoresis group

Results	% reduction in mPPASI score at 16 weeks	No of patients	Percentage
Excellent	100	14	70%
Good	75-100	4	20%
Moderate	50-75	-	-
Poor response	<50	2	10%

**Response to therapy in oral methotrexate group**

In Oral methotrexate group out of 20 patients 16 patients had complete clearance at 16 weeks and 4 had good

response. Therefore, in Oral Methotrexate group 80% of patients had excellent response and 20% of patients had good response at 16 weeks.

**Table 5:** Response to treatment in palmoplantar psoriasis in oral methotrexate group

Results	% Reduction in mPPASI score at 16 weeks	No of patients	Percentage
Excellent	100	16	80%
Good	75-100	4	20%
Moderate	50-75	-	-
Poor response	<50	-	-

**Discussion**

Psoriasis exclusively involving the palms and soles is known as palmoplantar psoriasis. Palmoplantar psoriasis can present as localized, isolated hyperkeratotic plaques or as pustules involving either palms or soles or both. There is often an overlap between the different morphological types making selection of treatment modality a difficulty. It leads to significant physical discomfort and dysfunction, resulting in disability [6]. Methotrexate is a dihydrofolate reductase inhibitor used in psoriasis since 1951. The usual dosage range from 0.2-0.4mg/kg/week. Bone marrow toxicity and liver toxicity are serious side effects of the drug [7].

Iontophoresis is a mode of transdermal drug delivery system using electric current to deliver soluble salts of particular drug into the tissues of the body for therapeutic purpose [8]. It can bypass the first pass metabolism and effectively deliver a drug without systemic side effects. Iontophoresis

enhances transdermal drug delivery by three mechanisms: (a) ion-electric field interaction provides an additional force that drives ions through the skin, (b) the flow of electric current increases the permeability of the skin, and (c) electro-osmosis produces bulk motion of solvent that carries ions or neutral species with the solvent stream [9]. Iontophoresis is widely studied in palmoplantar hyperhidrosis using tap water, poldine methyl sulfate, glycopyrronium bromide, and atropine. The FDA approved indications include iontophoretic delivery of fenatnyl, sumatriptan, lidocaine with epinephrine for post-operative pain, acute migraine and dermal analgesia respectively.

In our study most cases were in the age group of 20-50 years which correlated with study by Khandpur S *et al.* [10] The mean age of onset was around 45 years which was like study by Brunasso AMG *et al.* [11] Males were affected with palmoplantar psoriasis relatively more in number than

females which was in concurrence with study by Venkatesan A *et al.* [12] Both the palms and soles involvement showed higher frequency with 52.5% followed by soles alone (27.5%) and the palmar alone involvement with (17.5%) which was in accordance with Kumar B *et al* study.

The oral methotrexate group showed reduction in mean m-PPPASI from 31.23 at baseline to 0.47 at 16 weeks with percentage reduction of 98.49 at the end. Rajendran SN *et al* showed 98.4% reduction at 16 weeks. The iontophoresis showed reduction in mean m-PPPASI from 28.04 at baseline to 1.07 at 16 weeks with percentage reduction of 96.18% at the end. Haseena K *et al* showed 64.08% improvement with methotrexate iontophoresis at 12 weeks which was lower than our study which could be attributed to lower frequency of iontophoresis [5].

There was no statistical significance in the mean m-PPPASI between the two groups at 4,8,12 and 16 weeks stating that methotrexate iontophoresis was equally good as oral methotrexate in clearing the palmoplantar lesion. There were few limitations in our study like a small sample size and lack of control group. With the limitations aside, our study was the first to compare Oral methotrexate with methotrexate iontophoresis.

### Conclusion

The management of palmoplantar psoriasis using methotrexate iontophoresis showed comparable efficacy to oral low dose methotrexate.

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