

Topical Methotrexate for Treatment of Psoriasis: Formulation and Clinical Implications

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Summary:

Background: To test effectiveness and safety of topical methotrexate 0.5% gel and to introduce new formula of methotrexate gel using suitable media for delivery.

Patients and Methods: The clinical work was performed at the Department of Dermatology and Venereology in Baghdad Teaching Hospital during the period from January 2008 to October 2008. While preparation of formula was performed in the laboratories of the Department of Pharmacology- College of Medicine-University of Baghdad. Patients were divided in to two groups according to the type of treatment, group (I) 32 patients treated with methotrexate 0.5% gel and group (II) (placebo group) included 33 patients treated with placebo gel.

Results: A total of 65 patients with limited plaque psoriasis were included in this study. For the MTX group the mean PASI score before treatment was 7.07 while at 2, 4, 6 and 8 weeks treatment, it was decreased to 5.17, 3.93, 3.07 and 2.35 respectively. At eight weeks treatment 25(78%) patients achieved good response (reduction in PASI score \geq 50%), while 5(15.6%) patients achieved partial response (reduction in PASI score 25-49%) and 2(6.25%) patients had poor response (reduction in PASI score < 25%). For placebo group the pretreatment mean PASI score was 7.12 and after 2, 4, 6 and 8 weeks treatment it became 6.32, 6.07, 5.99 and 6.2 respectively. Clinically the response of the patients to placebo gel at 8 weeks treatment was partial in 10(30.3%) patients and poor in 23(69.7%) patients while no patients achieved good response.

Conclusions: MTX 0.5% gel is effective treatment option for plaque psoriasis and also appears to be safe treatment since side effects were transient, limited and reduced with continuation of therapy.

Key words: Psoriasis and methotrexate 0.5% gel

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Introduction:

Psoriasis is a common and complex disease affecting approximately 2% to 3% of the world population. This disease can manifest itself in the skin, as well as affect the nails and joints of patients (1, 2). In skin, nails, and joints, the fundamental pathological process underlying altered tissue structure and function is chronic inflammation (3,4). To avoid systemic toxicity, topical administration of methotrexate was attempted. Various studies demonstrate that methotrexate in suitable vehicle will produce direct effect on epidermis which is useful for the topical therapy of psoriasis (5). In various studies, penetration of methotrexate is enhanced with chemical enhancer which provides effective local inhibition of epidermal DNA synthesis in the in vivo hairless mouse and minipig models, providing biochemical rationale for topical use in the treatment of psoriasis (6). The site of action for topical MTX is the stratum spinosum and stratum germinativum (7).

Patients and Methods:

A total of 65 patients, 29 males and 36 females were included in this study. The study was conducted at the Department of Dermatology and Venereology-Baghdad Teaching Hospital during the period from January 2008 to October 2008. Patients were randomly divided into two groups according to type of treatment.

Group I: patients who were treated with MTX 0.5% gel; they were 32 patients.

Group II: patients who were treated with placebo gel; they were 33 patients. All the patients were interviewed and detailed history was obtained. Inclusion criteria include patients with stable plaque psoriasis involving less than 25% of the body surface area. While exclusion criteria include patients with psoriatic lesions on face and / or scalp, administration of topical, systemic or intralesional therapy or UV radiation for at least 2 months prior to the study, children, pregnant or lactating mothers, patients with evidence of hepatic and/or renal impairment and patients with psoriatic lesion more than 25% of the body surface area were excluded from this study.

Preparation of MTX gel: MTX gel was prepared in the laboratories of Department of Pharmacology in the College of Medicine-University of Baghdad. Preparation carried out by incorporation of

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methotrexate equivalent to 0.5% (w/w) in the base content. The general method employed for the preparation of bases was the fusion method which includes incorporation of methotrexate using spatula and slab (8).

Preparation of gel base: Preparation of sodium carboxymethyl cellulose (Na CMC) 5% w/w gel base is a modification for the other formulas of lubricating jelly formula and clear aqueous gel formula(9).

The base was prepared by mixing Na CMC with glycerin in a glass mortar, while methyl paraben was dissolved in 40 ml of distilled water using heat to about 70 C with vigorous stirring for 15 minutes and cooled, later the preparation was mixed with mixture and stirring until clear gel base was gained, the methotrexate then incorporated to the base with 5 minutes continuous triturating and stirring to obtain homogeneous clear drug – gel solution.

- Sodium Carboxy methyl cellulose (Na CMC)	5 gm
-Glycerol	15gm
-Methyl paraben	0.1gm
-Purified water up to	100gm

MTX gel was applied only to the psoriatic lesion and the patients were informed to recognize the sings of dermatitis, irritation or any other undesirable side effects.

Each patient was instructed to apply the formula once daily for eight weeks. All these instruction being followed during application of placebo gel. Each patient was assessed for the response to the topical therapy at two weeks intervals for eight weeks and at two weeks for one month of follow up period after stopping therapy to examine for any signs of relapse. Paired sample t-test and two sample t-test was used for comparison between variables (10). Data were analyzed on computerized program, Statistical Package for Social Science (SPSS version 11). P value of less than 0.05 was considered to be significant.

Results:

A total of 65 patients were completed this study; 29 males and 36 females, aged (17-55) years. the mean age was (31.93 ± 9.77) years [see table (1)]. The duration of disease ranged from three months to 25 years with a mean of (6.8 ± 5.7) years [see the table (2)]. Family history was positive in five (7.7%) patients. The MTX group (group I) included 32 patients aged (18-55) years. The mean age was (33.53 ± 10.08) years. Duration of disease ranged from 4 months to 22 years with mean of (7.71 ± 6.5) years. Thirteen patients were defaulted from the study for unknown reasons; in fact eight patients defaulted in the MTX group, while five patients defaulted from placebo group. The mean baseline PASI score was 7.07 while mean PASI score at 2, 4, 6 and 8 weeks of treatment were 5.17, 3.93, 3.07, and 2.35 respectively. Also PASI score for the first two weeks and second two weeks of follow up period was 3.25 and 3.53 respectively { figure (1) }.

The mean percent reduction at two weeks treatment was 25.41% , while at 4,6 and 8 weeks treatment it became 39.3%, 55.36%, 63.79% respectively {figure (3)}. At the end of treatment the response was shown in table (3), 25 (78%) patients achieved good response (reduction in PASI score $\geq 50\%$), while 5(15.6%) patients achieved partial response (reduction in PASI score 25-49%), and two(6.25%) patients had poor response. Five (20%) patients got relapsed at two weeks follow up and 2(8%) relapsed at the second two weeks. For the placebo group (group II) were included 33 patients was aged (17-48) years, with mean age (30.4 ± 9.36) years. Duration of disease ranged from two months to 18 years with mean of (6 ± 4.8) . The pretreatment mean PASI score was 7.12, but after 2, 4, 6 and 8 weeks treatment it became 6.32, 6.07, 5.99 and 6.2 respectively, and at the follow up period were 6.79 and 7.03 as shown in figure (2). The mean percent reduction of PASI score at two weeks treatment 11.26% while at 4, 6 and 8 weeks treatment were 14.71%, 15.9 % and 12.96% respectively. Clinically, the response of the patients to placebo gel was partial in 10(30%) and poor in 23(70%) while no patients achieve good response. Comparison of the mean PASI score at baseline of the MTX group with the placebo group showed no statistical significant difference between the two group ($P > 0.05$). While at the eight weeks treatment there is statistical significant difference between MTX group and placebo group ($P < 0.05$). Comparing the mean percent reduction in PASI score between the two groups. The MTX group achieved more percent reduction in PASI than placebo group through out treatment period ($P < 0.05$). Only 6 (three patients from each group) from 65 enrolled patients experienced adverse effects, which include: burning sensation, irritation, pruritis, and redness. But no patient stops treatment for these side effects. Hematological and biochemical laboratory tests were performed before and after treatment including complete blood count, liver chemistry (SGOT, SGPT) and serum creatinine all within the normal limit.

Table (1): The age in (years) for MTX group and placebo group:

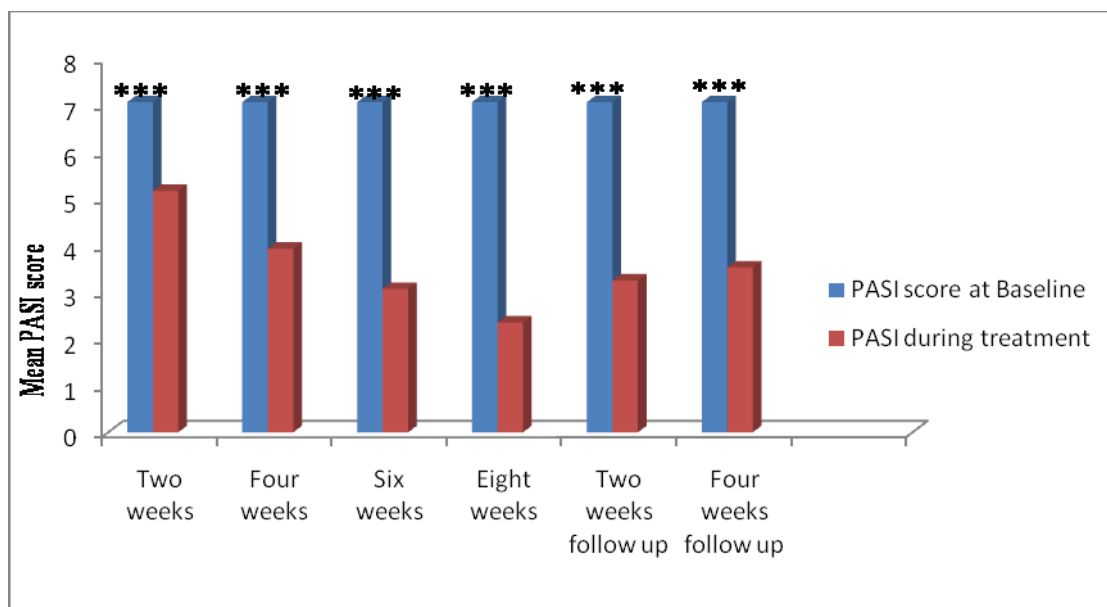
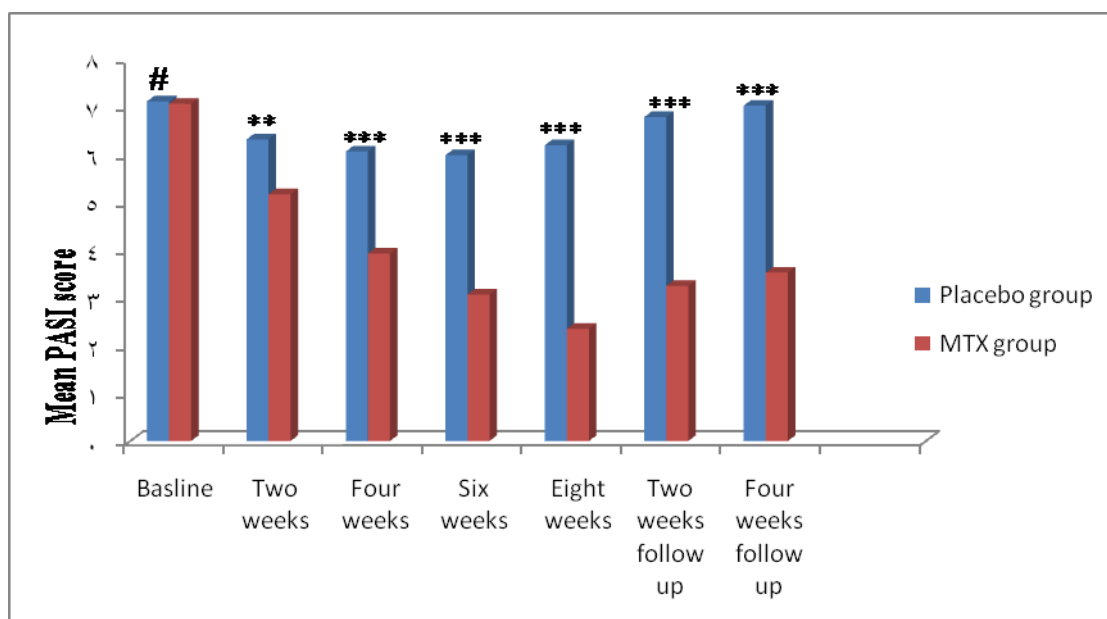
Age in (year)	MTX group		Placebo group	
	Number	Percent	Number	Percent
17-19	2	6.15	5	15.2
20-29	8	25	10	30.3
30-39	10	31.25	11	33.3
40-49	7	22	6	18.2
50-59	5	15.6	1	3
Total	32	100%	33	100%

Table (2): Duration of psoriasis in (years) in MTX group and placebo group:

Duration of psoriasis In year)	MTX group		Placebo group	
	Number	Percent	Number	Percent
Less than 1	2	6.25	4	12.12
1-5	13	40.6	14	42.42
6-10	12	37.5	8	24.24
11-15	2	6.25	4	12.12
16-20	2	6.25	2	6
21-25	1	3.12	1	3
Total	32	100%	33	100%

Table (3): Degree of response for the MTX group and placebo group at 8 weeks treatment:

Improvement	MTX group	Placebo group
Good response	25 (78.12%)	0 (0%)
Partial response	5 (15.62%)	11 (30%)
Poor response	2 (6.25%)	23 (70%)
Total number	32 (100)	33 (100%)


Figure (1): Mean PASI score during treatment and at follow up period for MTX group versus baseline. (*)P< 0.001).**

Figure (2): Comparison for the mean PASI score for MTX group and placebo group at the baseline, during treatment and at the follow up period.

#P> 0.05

**P< 0.01

***P< 0.001

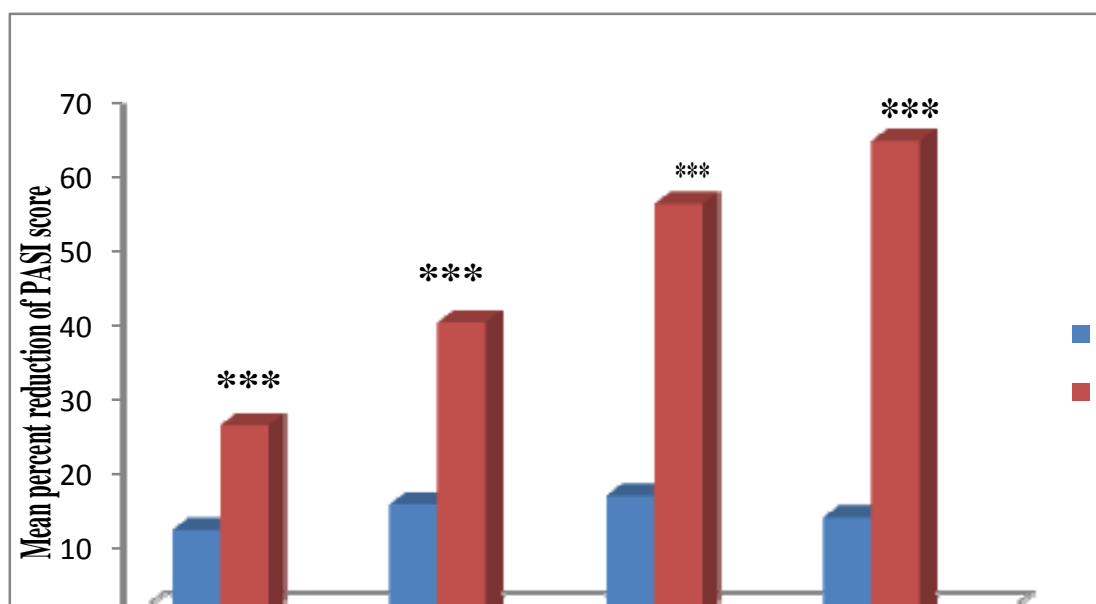


Figure (3): Comparison of the mean percent reduction of PASI scores during treatment with MTX 0.5% gel and placebo gel.
 (***) $P < 0.001$



Figure (3-4): A- Young man patient with plaque psoriasis before treatment.



B- After eight weeks of treatment with MTX gel.

Discussion:

Systemic MTX has been used in the treatment of generalized psoriasis for many years. It has achieved very good reputation, as the gold standard for treating generalized psoriasis (11). However its use is associated with risk for hematological and hepatotoxic side effects. Although patients with localized psoriasis have many treatment options, each option has its limitations and side effects (12). The use of topical MTX gel for treatment of psoriasis has been tried in earlier studies. However many authors stated that its action is not satisfactory (13, 14). Newer studies, however, have succeeded to induce remission by topical MTX (6, 15). Syed et al stated that MTX when incorporated in hydrophilic gel and applied topically for four weeks, induced 82% improvement versus 4.2% improvement in the placebo group. Various studies showed that after topical application of MTX gel there is significant amount of MTX was detected in the skin, indeed about (59%) of MTX found in the skin (in the stratum corneum) after one hour from local application (16, 17).

The poor results of the use of topical MTX reported by older reports (13, 14), may be related to the media used (ointment, cream and gel). MTX has poor solubility in the ointment base; the drug release from such formula is also low. In the creamy formula an oily layer will be deposited on the skin surface thus providing an additional barrier to the penetration of the drug. In the present study we focused on selecting appropriate gel base with physicochemical properties compatible with permeant and continuous phase (18). The penetration enhancer used in this study dimethylformamide (DMF) act through complex range of mechanisms; it acts by denaturing proteins, on application on human

skin it change the intercellular keratin from β -sheet conformation (19,20). In addition DMF act on intercellular lipid domains, it distorts the packing geometry of the barrier lipid. It was found the penetration enhancer interact with the stratum corneum to reduce the barrier properties of the membrane with out damaging the underling skin cells (18). On comparing topical MTX with other topical agent used in the treatment of psoriasis. Topical MTX 0.5% gel achieved comparable reduction in PASI score (64%) to topical betamethasone dipropionate (60%) (21). Calcipotriene ointment after eight weeks of treatment induced a mean percent reduction of PASI score 52.5% where the ointment applied once daily (21). The most common adverse reactions for topical calcipotriene were those related to irritation of skin (lesional, perilesional irritation), pruritus, burning and erythema, and scaling, especially in the facial and intertriginous areas. On comparing with coal tar, topical MTX gel appears more effective and more tolerable for the patients than coal tar, in which after eight weeks treatment with coal tar 5% ointment, the mean percent reduction of PASI score was only 45.8%(22). However coal tar in every form (ointment, cream, gel and lotion), is messy, stain the skin, and had a bad odor; other side effects include photosensitivity, acneform eruption, folliculitis and irritant dermatitis (23). In conclusion, MTX gel is effective treatment option for plaque psoriasis; also its safe treatment since side effects appear transient, limited, and disappear upon continuation of therapy. Finally other studies with larger number of patients to establish exact effective concentration of MTX in gel base and to study exact mechanism of action for topical MTX.

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