

Clinical Management Of Psoriasis Using 0.25% Niosomal Methotrexate Gel: A Placebo Controlled Double Blind Study

P Lakshmi, S Devi, S Bhaskaran, S Sacchidananda, Meenakshi

Citation

P Lakshmi, S Devi, S Bhaskaran, S Sacchidananda, Meenakshi. *Clinical Management Of Psoriasis Using 0.25% Niosomal Methotrexate Gel: A Placebo Controlled Double Blind Study*. The Internet Journal of Dermatology. 2004 Volume 3 Number 1.

Abstract

In the formulation of topical dosage forms, more attention has been devoted to new structures, which can ensure either adequate localization of drug within the skin to enhance the local effect or can increase the penetration through the stratum corneum. For these purposes vesicular systems such as niosomes and liposomes have been investigated by several groups. Drug delivery systems using colloidal particulate carriers such as liposomes or niosomes have distinct advantages over conventional dosage forms because the particles can act as drug containing reservoirs. Methotrexate (MTX) is used in psoriasis as a systemic therapy with lot of adverse effects. A novel sustained release niosomal 0.25% MTX using a polymer chitosan administered once daily for 12 weeks. It was compared with placebo gel and plain MTX 0.25% gel for the treatment of different types of psoriasis, especially palmoplantar psoriasis.

30 patients were enrolled for study. They were divided randomly in to three groups of 10 patients for each formulation. The patients with 25% or less than 25% psoriatic lesions were included for the study.

The results are calculated using PASI scoring. Changes in the disease signs and symptoms indicated that both agents have anti psoriatic activity but not with placebo gel. However lesions treated with Niosomal chitosan-MTX formulation showed marked improvement in comparison to plain MTX and placebo gel inspite of twice a day application. Few patients experienced mild adverse events. No clinically significant changes in blood or other lab parameters were seen.

The findings suggest that the 0.25% niosomal MTX in chitosan gel exhibited beneficial effect in psoriasis and did not exert any systemic toxicity.

BACKGROUND

Psoriasis is a common noninfectious chronic inflammatory skin disorder characterized by well defined, distinctive erythematous plaques that produce adherent silvery white scales which may cause bleeding points when removed (auspitz's sign). Psoriasis may flare up at any cutaneous surface but most frequent sites are the extensor surfaces of the elbows and knees, scalp and sacral areas₁. Methotrexate (MTX) is frequently used orally in the treatment for severe, recalcitrant psoriasis. Although effective, MTX has the potential to induce hepatotoxicity, bone marrow suppression, and other adverse effects, thus limiting its use for systemic therapy. To minimize the systemic exposure and toxicity associated with orally administered MTX, topical MTX formulations containing Azone (laurocapram), a skin penetration enhancer are being developed and evaluated₂.

Earlier study of MTX (0.1,0.5,and1%) in Azone formulation produces a 50% or greater improvement in psoriatic patients following 6 weeks twice daily application. Inorder to have better skin penetration and also sustained effect to improve the patient compliance a novel drug delivery using niosomal methotrexate incorporated in chitosan polymer in the form of gels were used as once daily application₃.

Niosomes or non-ionic surfactant vesicles are now widely studied as an alternative to liposomes and produces sustained release of drug topically. An increasing number of non-ionic surfactants have been found to form vesicles capable of entrapping hydrophobic and hydrophilic solutes. These non-ionic surfactant vesicles are regarded either as inexpensive alternatives, of non-biological origin, to liposomes, or perhaps in vivo as a carrier system to carry drug molecules like liposomes_{4,5}.

Chitosan, a natural polysaccharide, is being widely used as a pharmaceutical excipient. It is obtained by the partial deacetylation of chitin, the second most abundant natural polymer. The presence of a number of amino groups permit chitosan to chemically react with anionic systems, thereby resulting in alteration of physicochemical characteristics of such combinations. The polymer has also been investigated as a potential adjuvant for swellable controlled drug delivery systems. Chitosan exhibits myriad biological actions, namely hypocholesterolemic, antimicrobial and wound healing properties. Hence this property can be exploited for the treatment of psoriasis and controlled release topical formulation can be made using chitosan ⁶.

On MTX, only few studies are available on topical formulation. The adverse effects of oral MTX can be avoided by using the topical preparations. The controlled release of niosomes will enhance the stay of the drug on the site and will provide better therapeutic effect. Topical formulation MTX will be a boon to the psoriasis patients. Polymers like Chitosan has been used which has anti-inflammatory effect and penetration enhancing effect so that better absorption can be obtained ^{8,9}.

Topical drug delivery is important from the viewpoints of improvement of therapeutic effect and reduction of systemic side effects¹⁰. Hence niosomal MTX-chitosan gel is formulated and studied on psoriatic patients.

MATERIAL AND METHODS

HUMAN REPEATED INSULT PATCH TEST (HRIPT)

STUDY PROCEDURE

This was performed on human volunteers to determine the irritation and/or allergic contact sensitization potential of a test article after repetitive patch applications to the skin of human subjects before subjecting formulations on patients ¹¹. 10 human volunteers selected for the study. Approval was obtained from ethical clearance committee of the hospital to conduct human volunteer study. An informed consent from the human volunteer had been obtained before starting the study. Human volunteers were randomly assigned. Table 1 provides the sex and age distribution of the human volunteers.

Figure 1

Table 1: Demographic features of human volunteers

N=10		Placebo	Plain MTX* 0.25%gel	Niosomal MTX* 0.25%gel
Sex	F*	30 %	30 %	30 %
	M**	70%	70%	70%
Age		31.08± 10.132	31.08± 10.132	31.08± 10.132

* Female; ** Male

INDUCTION PHASE

Approximately 0.2 grams of each gel is applied to the subject's back, using occlusive patches. Semi-occlusive tape was applied. Twenty-four hour patch applications were made on a Monday, Wednesday, Friday schedule. Twenty-four hour rest periods follow Tuesday and Thursday removals and a 48-hour rest period follows the Saturday removal. The site was scored by a dermatologist just prior to the next patch application. This procedure was repeated until 9 inductions of the test article are made on the same skin site.

The area was scored with 0-5 point scale. If a subject develops a level 2 reaction or greater during the Induction phase, the patch was applied to an adjacent fresh site for the next application. If a 2 or greater reaction occurs on the new site, no further induction applications were made. However, any reactive subjects are subsequently patched with the test article on a virgin test site during the challenge phase of the study.

CHALLENGE PHASE

Approximately 2 weeks after application of the last induction patch, a challenge patch was applied to a previously unpatched (virgin) site, adjacent to the original induction patch site. The challenge site was scored 24 and 72 hours after application. The subjects were asked to report any delayed reactions, which might occur after the final challenge patch reading. The results are tabulated in Table 2

Figure 2

Table 2: Frequency of dermal response in Human Repeated Insult Patch Test at each evaluation interval

Formulation	Observed Reaction	Induction Phase Readings (24hrs) (N=10)										Challenge phase readings	
		Ind1	Ind2	Ind3	Ind4	Ind5	Ind6	Ind7	Ind8	Ind9		cha1 (24hrs)	cha2 (72hrs)
Placebo	0	100%	100%	100%	100%	100%	100%	100%	100%	100%		100%	100%
	1	0	0	0	0	0	0	0	0	0		0	0
Plain gel	0	100%	100%	100%	100%	100%	100%	100%	100%	100%		100%	100%
	1	0	0	0	0	0	0	0	0	0		0	0
Niosomal gel	0	100%	100%	100%	100%	100%	100%	100%	100%	100%		100%	100%
	1	0	0	0	0	0	0	0	0	0		0	0

Ind-Induction; Cha-Challenge

Skin responses are scored according to the following 6-point scale:

1. (None) No evidence of any effect.
2. (Barely perceptible) Minimal, faint, uniform or spotty erythema.
3. (Mild) Pink, uniform erythema covering most of the contact site.
4. (Moderate) Pink-red erythema, uniform in the entire contact site.
5. (Marked) Bright red erythema with/without petechiae or papules.
6. (Severe) Deep red erythema with/without vesiculation or weeping.

None of human volunteers faced any irritation during induction and challenge phase. Hence results of level 2 to level 5 are not shown Table 2. These formulations were used for patient study.

DOUBLE BLIND PLACEBO CONTROLLED PASI STUDY ON PSORIASIS PATIENTS

The extent and severity was measured by Psoriasis Area and Severity Index (PASI). Global assessment was measured for efficacy, tolerability of the treatment, and the preference between the treatments administered^{3, 12}.

PATIENT POPULATION

30 patients between ages of 22 and 50 years having psoriasis from 2- 8 years were chosen for inclusion in the study. Approval was obtained from ethical clearance committee of the hospital to conduct patient study. An informed consent from the patient had been obtained before starting the study. Patients were randomly assigned to study the treatments. All the patients were evaluated for the efficacy of the treatments. All the 30 patients completed the full study. Table 3 provides demographic features of patients participated in the study.

INCLUSION CRITERIA

Patients with stable plaque psoriasis involving <25% of the body surface area and palmoplantar psoriasis.

EXCLUSION CRITERIA

Patients with psoriatic lesions on face and or scalp, administration of other systemic therapy or intralesional therapy or UV radiation for atleast 2 months prior to inclusion in the study, children, pregnant and lactating

mothers, Patients with above 25%lesions were excluded from the study.

METHOD

Extent and severity as measured by psoriasis and severity index (PASI) using a method described by Lynda Sutton BS et al.,³. Global assessment was measured for efficacy and tolerability of the treatment, preference between the treatments administered. The global assessment was done on a 0-5 ordinal scale ranging from completely clear to worse. The severity of the erythema, infiltration, desquamation and overall severity was assessed presence of lesion on the trunk, upper arm or lower arm. The PASI score was calculated as the sum of severity of main symptoms multiplied by the numerical value of the areas involved with various percentages of the 3 main body areas. The scoring was done depends on the area of the lesion.

FREQUENCY OF THE CLINICAL EVALUATION

The efficacy of the treatment was evaluated as baseline (time 0) and subsequently for every 2 weeks for 12 weeks.

Figure 3

Table 3: Demographic features of patients participated in double blind placebo controlled PASI study

N=10		Placebo gel	Plain 0.25% MTX gel	Niosomal 0.25% MTX gel
Sex	F*	30 %	60%	50%
	M**	70%	40%	50%
Age		41.78± 11.032	34.33± 11.032	38.67± 11.032.
Duration of psoriasis		4.389±6.1021	4.222± 1.7341	4.537± 1.6667

*Female

**Male

(Age and the duration of psoriasis were not significantly (P<0.05) different from each other)

PATIENT STUDY PROCEDURE

The study is a single center, double blind placebo controlled, comparison of treatments.

Patients were given placebo and plain gel twice-daily application. Niosomal MTX gel was given once a day application and placebo gel was given to this niosomal group to apply at night to avoid the bias between the placebo and plain gel groups. The body surface area treated ranged from and the formulations were applied in quantities of approximately 50g/m². Treated lesions were a maximum of 25% of the body surface area.

RESULTS

The gels were subjected for HRIPT test on human volunteers to study the irritation on the skin. None of the formulations

selected for the patient study had produced irritation. The patient study also revealed that only few patients had experienced mild adverse events, which were of local in nature such as burning irritation. There were no clinically significant changes in hematologic or clinical laboratory features in any patient.

Figure 4

Table 4: provides the results PASI scoring of all the formulations.

Treatment period follow-up (N=10)	Placebo	Plain MTX gel	Niosomal MTX gel
Week 2	4.2±0.228	4.0±0.55	4.1±0.226
Week 4	4.2±0.228	3.8±0.326	3.4±0.726
Week 6	4.2±0.228	3.7±0.213	3.3±0.126
Week 8	4.4±0.108	3.4±0.101*	3.0±0.216*
Week10	4.3±0.228	3.2±0.122	2.6±0.316
Week12	4.2±0.212	2.6±0.212	1.7±0.316**

In comparison to MTX 0.25%plain gel, the niosomal gel once a day application was found to be superior enhancing the patient compliance. There was a significant difference (P<0.05) between the placebo, plain gel and the niosomal MTX gel.

The change in the disease status from baseline was consistent with changes in disease signs and symptoms. Both the treatment produced good result but niosomal gel produced better result compared to placebo and plain gel (P<0.05). None of the placebo treated lesions were improved at the end of the treatment.

Figure 5

Table 5: Mean change (±standard deviation) in psoriasis severity scores from baseline

Treatment period Follow up(N=10)	Total psoriasis score			Erythema score		
	Placebo	Plain MTX gel	Niosomal MTX gel	Placebo	Plain MTX gel	Niosomal MTX gel
Baseline	2.056±0.928	2.006±0.401	2.008±0.742	0.656±0.269	0.648±0.020	0.632±0.273
Week 2	2.06±0.924	1.584±0.300	1.202±0.777	0.656±0.269	0.422±0.026	0.410±0.273
Week 4	1.993±0.948	1.452±0.566	1.032±0.769	0.589±0.310	0.320±0.212	0.300±0.273
Week 6	1.96±0.964	1.421±0.566	0.908±0.784	0.556±0.357	0.302±0.122	0.262±0.303
Week 8	1.915±1.012	1.374±0.416	0.745±0.651	0.511±0.401	0.292±0.102	0.222±0.250
Week 10	1.915±1.096	1.278±0.534	0.470±0.271	0.511±0.401	0.196±0.222	0.152±0.248
Week 12	2.133±1.165	1.132±0.315	0.282±0.319	0.511±0.401	0.092±0.123	0.060±0.212

Figure 6

Table 6: Mean global improvement score (± standard deviation)

Treatment period Follow up(N=10)	Infiltration score			Desquamation score		
	Placebo	Plain MTX gel	Niosomal MTX gel	Placebo	Plain MTX gel	Niosomal MTX gel
Baseline	0.76±0.403	0.734±0.122	0.744±0.264	0.644±0.292	0.624±0.259	0.632±0.205
Week 2	0.76±0.403	0.636±0.132	0.37±0.255	0.644±0.292	0.526±0.142	0.422±0.249
Week 4	0.76±0.403	0.606±0.212	0.31±0.247	0.644±0.292	0.526±0.142	0.422±0.249
Week 6	0.76±0.403	0.606±0.212	0.29±0.267	0.644±0.292	0.513±0.232	0.356±0.213
Week 8	0.76±0.403	0.590±0.192	0.19±0.162	0.644±0.292	0.501±0.122	0.333±0.240
Week 10	0.76±0.403	0.590±0.192	0.14±0.151	0.644±0.292	0.492±0.020	0.178±0.120
Week 12	0.70±0.464	0.560±0.182	0.12±0.199	0.652±0.295	0.480±0.010	0.102±0.120

0=cleared; 1=marked improvement; 2=moderate improvement; 3=slight improvement

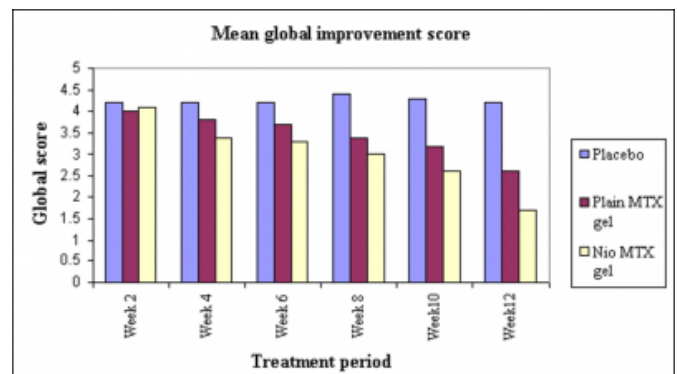
4=no change 5=worse

• A trend towards significant difference (P<0.05) between active and the placebo treatment.

** A significant difference (P<0.05) between plain gel, Niosomal gel and placebo.

Figure 7

Figure 1: Mean Global improvement score



DISCUSSION

Complete patient compliance was achieved with the study medication. The Placebo, plain, niosomal gel preparations was well tolerated by all the patients and there were no dropouts. All 30 patients completed 12 weeks study. There was reduction in erythema followed by slight reduction in infiltration and desquamation leading to moderate to excellent improvement seen. There was substantial reduction in PASI score from the initial level.

Demographically all the three groups patients were comparable in age sex, presence of less than 25% of the psoriasis and the duration of psoriasis. Patients of stable plaque psoriasis with less than 25% and palmoplantar psoriasis were included for the study to avoid the use of this anticancer drug and to avoid more area exposed to this medication available for systemic absorption. Periodic

routine laboratory tests including complete blood count, urine analysis, liver chemistry (SGOT and SGPT) and serum creatinine were within normal limits

Consistent with previous studies the results of this study indicate that niosomal MTX formulated with chitosan applied topically is effective in treating psoriasis. Especially palmoplantar psoriasis. The study on human volunteers also reveals that it does not produce any skin irritation and MTX can exert local therapeutic effect. Further various percentages of MTX has to be optimized for more clinical effectiveness.

The major findings of the study reveals that the niosomal MTX (0.25%) in a chitosan gel used as a topical agent significantly resolved psoriatic lesions and was shown to be quite effective in treating patients without any side effects. This gel was used once a day regime in comparison to plain preparation, which is, used twice a daily.

Most of the current treatment either topical or systemic involves suppression of diseases with lot of side effects and patient compliance is questionable. In this case the niosomal MTX in chitosan gel provides once a day application for patients by improving adherence to treatment.

This regimen can be an alternative treatment modality for treatment of psoriasis.

CORRESPONDENCE TO

P.K.Lakshmi. M.Pharm, (PhD) Dy. Director-Drug Information Karnataka state pharmacy council 514/E, I main, II stage, Vijayanagar club road, Vijayanagar Bangalore, Karnataka-560 040 Ph. 11-080-23383142,

11-080-23404000, Fax: 11-080-23202345 Email: sureshlakshmi6@yahoo.com

References

1. Weinstein GD, Van Scott EJ. Auto radiographic analysis of turnover times of normal and psoriatic epidermis. *J Invest Dermatol* 1965;45:257-62.
2. Weinstein GD, McCullough JL, Olsen E: Topical methotrexate therapy for psoriasis. *Arch Dermatol* 1989;125:227-230.
3. Lynda Sutton BS et al. A clinical study to determine the efficacy and safety of 1% Methotrexate / azone (MAZ) gel applied topically once daily in patients with psoriasis vulgaris. *Int.J.of dermatol* 2001;40:464-467.
4. Aliasgar Shahiwala, Ambikanandan Misra, Studies in topical application of niosomally entrapped Nimesulide, *J Pharm Pharmaceut Sci* (<http://www.ualberta.ca/~cspss>). 2002;5:220-225.
5. Azmin MN, Florence AT, Handjani-Vila RM, Stuart JF, Vanlerberghe G, Whittaker JS. The effect of non-ionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice, *J Pharm Pharmacol*. 1985;37:237-42.
6. Ravi Kumar MNV, Neeraj Kumar, Polymeric controlled drug delivery systems: Perspective issues and opportunities, *Drug Dev. Indust. Pharm.*, 2001;27:1-30.
7. Illum L, Chitosan and its use as a pharmaceutical excipient, *Pharm. Res.* 1998, 15: 1326-1331.
8. Ravi Kumar MNV, Nano and Microparticles as controlled drug delivery devices, *J.Pharm. Pharmaceut. Sci.*, 2000(2);3:4-5.
9. Dodane V, Khan MA, Merwin JR, Effect of chitosan on epithelial permeability and structure, *Int. J. Pharm.* 1999;182:21-32.
10. Yie W Chien, Novel Drug Delivery System in Transdermal Drug Delivery & Delivery System, 2nd Rev Ed, Marcel Dekker Inc., USA, 1982;200-213.
11. Tardiff RG, Hubner RP, Graves CG. Harmonization of thresholds for primary skin irritation from results of human repeated insult patch tests and laboratory animal skin irritation tests, *J Appl Toxicol*. 2003;23:279-81.
12. Kirby B Richards HL et al. Physical and psychological measures are necessary to assess overall psoriasis severity. *J Am Acad Dermatol*. 2001;45:72-76.

Author Information

P. K. Lakshmi, M.Pharm, (PhD)

Dy.Director-Drug Information, Karnataka state pharmacy council

S. Gayathri Devi, PhD

Al-Ameen College of Pharmacy

Shyamala Bhaskaran, PhD

Al-Ameen College of Pharmacy

S. Sacchidananda, MD, DVD

Department of Skin & STD, Victoria hospital

Meenakshi, MBBS

Department of Skin & STD, Victoria hospital