Klinik ve Deneysel Araştırmalar Dergisi /
Journal of Clinical and Experimental Investigations

Cilt/Vol 1, No 3, 143-149

ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

Effectiveness of oral zinc sulphate, oral methotrexate and their combination in the treatment of psoriasis

Psöriazis tedavisinde oral çinko sülfat, oral metotreksat ve ikisinin kombinasyonunun etkinliği

Jawad H. Ahmed[1], Saad Raheem Abd[2], Khalil I.Al-Hamdi[3]

[1]Department of Pharmacology, College of Medicine, University of Basrah, Iraq.
[2]Al-Nasria Teaching Hospital, Iraq
[3]Department of Dermatology, College of Medicine, University of Basrah, Iraq

ABSTRACT

Objectives: To evaluate the effectiveness of oral zinc sulphate in treatment of psoriasis alone or in combination with methotrexate.

Materials and methods: A Total of 60 patients with psoriasis vulgaris were recruited for the study during the period October 2006 to October 2007. The patients were divided in to three groups according to their systemic treatments, as follows: Patients in Group1 (20 patients) were treated with oral zinc sulphate, Group 2 (20 patients) were treated with zinc sulphate plus oral methotrexate and patients in Group 3 (20 patients) were treated with oral methotrexate alone.

Results: There were 34 (56.7%) men and 26 (43.3%) women, with a male: female ratio 1.3:1.Their age ranged from 15-70 years with a mean of 32±11 years. Oral zinc sulphate produced a good response in about 60% of the cases; with a relapse rate amounts to 58% noticed 4 weeks after cessation of treatment. Combination of oral zinc sulphate and methotrexate induced a good response in 85% of the patients, with a relapse rate of 59 % that was noticed 4 weeks after treatment cessation. Methotrexate alone induced a good response in 70% of the patients with a relapse rate of 64%. Mild adverse effects were reported in 30% of the cases on zinc sulphate treatment.

Conclusion: Zinc sulphate is an effective treatment of psoriasis but the combination of zinc sulphate plus methotrexate could be more effective than zinc sulphate or methotrexate alone. *J Clin Exp Invest 2010; 1(3): 143-149*

Key words: psoriasis, zinc sulphate, methotrexate, treatment, relapse

ÖZET

Amaç: Bu çalışmanın amacı, oral çinko sülfatın psoriazis tedavisinde tek başına ve metotreksat ile kombine edildiğinde etkinliğini araştırmaktır.

Gereç ve yöntem: Toplam 60 psöriazis vulgaris'li hasta Ekim 2006 - Ekim 2007 tarihleri arasında çalışmaya alındı. Hastalar sistemik tedavilerine göre aşağıdaki gibi üç gruba ayrıldı: Grup 1 (20 hasta) oral çinko sülfat ile tedavi edilenler; Grup 2 (20 hasta) oral çinko sülfat+ oral metotreksat ile tedavi edilenler ve Grup 3 (20 hasta) tek başına oral metotreksat ile tedavi edilenler.

Bulgular: Çalışmaya 34 (%56.7) erkek ve 26 kadın (%43.3) hasta (Erkek/Kadın oranı: 1.3/1) alındı. Oral çinko sülfat alan grupta hastaların yaklaşık %60'ında iyi sonuç alındı ve bu grupta tedavi kesilmesinden 4 hafta sonra hastaların %58'inde relaps gelişti. Oral çinko sülfat+Oral metotreksat kombinasyonu hastaların %85'inde iyi sonuç verdi ve tedavi kesilmesinden dört hafta sonra bu grupta %59 oranında relaps gözlendi. Tek başına metotreksat %70 hastada iyi sonuç verdi ve bu grupta tedavi kesilmesini takiben %64 hastada relaps gelişti. Oral çinko sülfat grubunda %30 hastada hafif yan etkiler gözlendi

Sonuç: Çinko sülfat psöriazis tedavisinde etkilidir, ancak çinko sülfat+Metotreksat kombinasyonu tek başına çinko sülfat veya metotreksat'tan daha etkili gözükmektedir. *Klin Den Ar Derg 2010; 1(3): 143-149*

Anahtar kelimeler: Psöriazis. çinko sulfat, metotreksat, tedavi, tekrarlama

Yazışma Adresi /Correspondence: *Dr. Jawad H. Ahmed, Department of Pharmacology, College of Medicine, University of Basrah, Iraq.* **Email:** jawadahmed_basmed@yahoo.com
Geliş Tarihi / Received: 30.09.2010, Kabul Tarihi / Accepted: 17.11.2010

INTRODUCTION

Psoriasis is a common relapsing, non infectious genetically determined disease.[1] Various drug regimens are used with variable benefit. Among these synthetic steroids which is effective and rapidly clearing skin lesions but this treatment is associated with distressing side effects, moreover relapses occur if treatment withdrawal is attempted.[2] Other treatments are either expensive and having even more severe side effects such as retinoids, hydroxyurea, methotrexate[3] infliximab[4] and others. Oral zinc supplementation has been tried in various skin diseases. While benefical effects were obtained in psoriatic arthritis[5] and in acne vulgaris[6] no effect was reported in atopic eczema[7] and in chronic plague psoriasis[8] The present study, therefore aimed to evaluate the effect of oral zinc supplementation alone or in combination with methotrexate in patients with plague psoriasis.

PATIENTS AND METHODS

Study design

This is an open-label, therapeutic, outpatient-based study that enrolled 68 patients with moderate to severe psoriasis vulgaris (plague psoriasis). All patients were selected during their consultation to the Department of Dermatology and Venereology at Basrah Teaching Hospital and AL-Nasirryah General Hospital during the period from October 2006 to October 2007. The study protocol was explained to the patients and written informed consents were obtained from all of them prior to their entry to the study. The study was approved by the Local Ethical Committee. Eight patients were withdrawn and sixty patients completed the study.

The patients were divided into three groups according to their systemic treatment modalities: The patients in group 1 (n= 20) were treated with oral zinc sulphate (220 mg twice daily). Group 2 (n= 20); patients on oral zinc sulphate (220 mg twice daily) plus oral methotrexate (15 mg/week), and patients in group 3 (n= 20) were treated with oral methotrexate (15 mg/week) alone. Treatment for the three groups continued during 12 weeks.

The diagnosis of psoriasis was made based on clinical examination. Psoriasis was classified as mild if the Psoriasis Area and Severity Index (PASI) scores below 10, and moderate to severe if PASI equal 10 or above.[9] Men and women in the age range between 15 and 70 years with moderate and severe psoriasis were included in the study. Patients were rejected if they are pregnant women, mild psoriasis and/or anemic. Those patients who were on topical or systemic treatments were asked to stop their treatments two weeks prior to the study and were kept on Vaseline ointment as emollient agent. Patients assigned to receive Methotrexate were given additional folic acid 5 mg/day, in order to prevent methotrexate induced nausea without interfering with the beneficial effects of the drug on psoriasis.[10]

All patients were interviewed, detailed history including, age, sex, occupation, residence, duration of disease, medical history, family history, seasonal variations, history of previous treatment and smoking were obtained. The patients were investigated for complete blood count, liver enzymes, blood urea and serum creatinine and were asked to come to the clinic for follow up every two weeks for 12 weeks. During these visits the following measurements were made:

Laboratory studies

Serum level of zinc was measured by a special kit.[11] For each patient a baseline corrected value of zinc was obtained by subtracting the value of zinc obtained at the end of 12 weeks treatment from the corresponding baseline values of zinc. The difference in zinc levels were then correlated with % reduction from baseline values of PASI Score after 12 weeks treatment.

Clinical assessments (PASI- score)

PASI score was employed to evaluate the extent of the disease and to monitor the therapeutic response. PASI score was measured before, during and after treatment.[12] Evaluation of the response after 4, 8 and 12 weeks of treatments is presented as % reduction from baseline values of PASI Score.

The patients were arbitrarily divided into three groups according to their response to treatments; those who achieved a reduction in PASI Score $\geq$ 50% (good response), 25-49% (poor or no response).

Statistical analysis

Statistical analyses were performed using by a computer program. Data were expressed as mean±SD. Kruskal-Wallis test was used to investigate difference of continuous variables between three groups.

Differences between means of two groups were tested by Mann-Whitney U test, and Chi-square was used where appropriate. P value less than 0.05 was considered significant.

RESULTS

Sixty patients completed the study. Thirty four (57%) patients were men, with a mean age of (32.6 ± 13 years) and 26 (43%) were women with a mean age of (31.5± 9.9 years). Their ages ranged from 16-70 years. With a male: female ratio of 1.3:1. Family history (both father and mother) of psoriasis was positive in 32 patients (53%). Nail changes were found in 52% of patients. Itching was reported in about 75% of patients which varied in severity from mild to severe. Itching was mild in about 30% of patients, while it was moderate and severe in 23%, and 22% of them respectively.

Twenty five patients (42%) were smokers, all of smokers were men. Emotional factors were blamed as an aggravating factors in 33 (55%) of patients. Seasonal variations were involved in the exacerbation of the disease. Thirty two patients (53%) reported an increase in the severity of the disease in winter, while 18 patients (30%) reported an increase in the severity of their disease during summer and only in 10 patients (17%) the disease is severe in the spring.

Clinical assessment of the response to treatments

The mean baseline value of PASI score in the patients who were assigned to receive oral zinc sulphate 220 mg twice daily (group 1) was 11.5±6.6. The values of PASI score started to decline as treatment continued, and at the end of 6, 8, 10, and 12 weeks of treatment the mean values of PASI score became 8.5±5.3, 7.4±4.9, 6.9±4.9 and 6±5, respectively. These values were significantly different from that of the baseline (Table 1).

The mean baseline value of PASI score in patients who were treated with the combination oral zinc sulphate and methotrexate was 11±6.4 (group 2) which was declined to levels of 7.4±4.4, 6±4, 4.8±3.7, 4.2±3.5, and 3.7±3.4 at the end of 4, 6, 8, 10, and 12 weeks of treatment respectively (Table 1).

Similar pattern of reduction in PASI score was also observed with oral treatment of methotrexate alone (15 mg/week) (group 3). The mean value of PASI score declined from 13.3±7.1 to 5.3±4 at the end of 12 weeks of treatment (Table 1).

In order to show the magnitude of change in PASI score the data were presented as % reduction from baseline values of PASI Score (Table 2). The mean value of % reduction from baseline values of PASI Score in patients on oral zinc sulphate alone at week 4 of treatment was 22+10.6%. This was significantly reduced to 38+12 at 8 weeks and to 53.7+19.7 at 12 weeks treatment. The mean values of the %reduction at 8 and 12 weeks were significantly different from that of the 4 weeks values ($P<0.05$).

On the other hand, the mean value of % reduction from baseline values of PASI Score at week 4 of the combination treatment oral zinc sulphate and methotrexate was 31.4 ± 14.6%. Further reduction was observed as treatment continued, the mean value of reduction became 54.5 ± 19.5% at the end of 8 weeks and 66.7±19.7 % at the end of 12 weeks treatment and both of these values were significantly different from that of the 4 weeks values (Table 2).

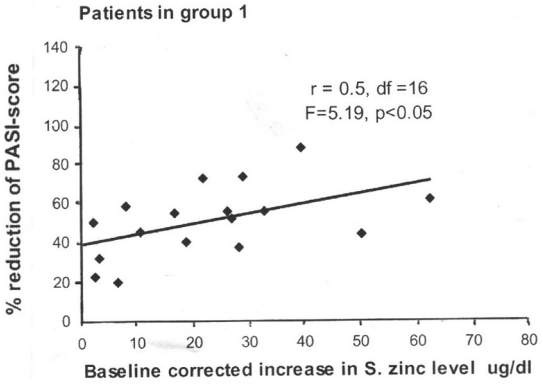

Figure 1a

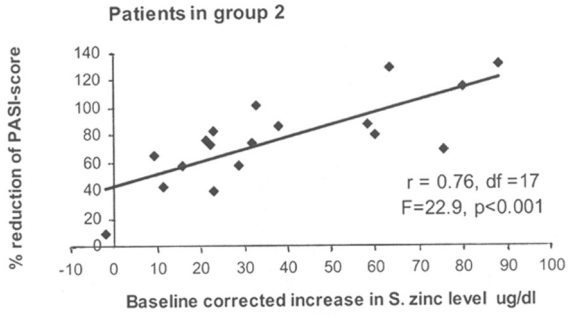

Figure 1b

Figure 1. Association between differences in serum zinc levels at 12 weeks (baseline corrected) and % reduction from baseline values of PASI score for patients treated with zinc sulphate alone (Group 1, **Figure 1a**) and for the combination therapy (Group 2, **Figure 1b**).

Table 1. The effect of treatments on PASI Score (Mean± SD) at 4, 8 and 12 weeks in treatment groups.

Weeks	Zinc Sulphate (n=20)	Zinc sulphate+ Methotrexate (n=20)	Methotrexate (n=20)
Baseline	11.5±6.6	11.0 ± 6.4	13.3 ± 7.1
2	11.4±6.6	10.9 ± 6.2	12.4 ± 6.9
4	9.1 ± 5.4	7.4 ± 4.4*	9.7± 5.3
6	8.5 ± 5.3*	6.0 ± 4.0*	8.1± 4.9*
8	7.4 ± 4.9*	4.8 ± 3.7*	6.4 ± 4.3*
10	6.9 ± 4.9*	4.2 ± 3.5*	5.9 ± 4.2*
12	6.0 ± 5.0*	3.7 ± 3.4*	5.3 ± 4.0*

* significantly different (P-value < 0.05) from the corresponding baseline value

Table 2. Reduction percentage from the baseline corrected PASI score at the end of 4, 8 and 12 weeks following treatments (Mean ± SD)

Weeks following treatments	Zinc Sulphate (n=20)	Zinc sulphate+ Methotrexate (n=20)	Methotrexate (n=20)
4 weeks	22 ± 10.6%	31.4 ± 14.6%	25.9±19.9%
8 weeks	38 ± 12%*	54.5 ± 19.5%*	48.6±19.9%*
12 weeks	*53.7±19.7%*	66.7 ± 19.7%*	59.3±21.3%*

* Significantly different from the corresponding 4 weeks values P< 0.05

Moreover, the mean value of % reduction from baseline values of PASI Score in patients on methotrexate alone at week 4 of treatment was 25.9±19.9%, this was significantly reduced to 48.6±19.9 and 59.3±21.3 at 8 and 12 weeks respectively (P<0.05). Although the mean value of % reduction from baseline value of PASI score for the combination treatment was 66.7±19.7% which was slightly higher than that of the oral zinc sulphate or methotrexate treatment but the differences between the three groups at week 12 of treatment were not reached to a statistically significant level.

At the end of 12 weeks of treatment 85% of patients who were treated with the combination of oral zinc sulphate (220 mg/twice daily) and methotrexate (15 mg/week) achieved a good response to the treatment while 60% and 70% of patients achieved a good response on monotherapy of oral zinc sulphate or methotrexate respectively. The percentage of patients who had shown poor or no response was 15%, 40%, and 30% for patients on the combination oral zinc sulphate-methotrexate, monotherpy of oral zinc sulpahate or methotrexate monotherapy respectively (Table 3). The onset of response was marked after 4 weeks of treatment with the combination of oral zinc sulphate and methotrexate, while the same response was achieved at 6 and 8 weeks after monotherapy with methotrexate or zinc sulphate respectively.

Table 3. The degree of response to various treatments after 12 weeks of treatment and relapse after cessation of treatment

	Zinc sulphate n (%)	Zinc sulphate + Methotrexate n (%)	Methotrexate n (%)
Good response*	12 (60)	17 (85)	14 (70)
No response**	8 (40)	3 (15)	6 (30)
Relapse			
Relapse rate	7 (58)	10 (59)	8 (64)

* reduction in PASI score ≥ 50%, ** reduction in PASI score between 25-49%

Relapse rates

Four weeks after cessation of treatment the disease has relapsed in 7 patients out of 12 patients who had shown a good response on treatment with oral zinc sulphate, the relapse rate was calculated to be 58%. The relapse rate was 59% for the patients on the combination zinc sulphate and methotreaxate, while the relapse rate after monotherapy with methotrexate was slightly higher than in patients in the other two groups (64%). There were no significant differences in the % of relapse rate between the three treatment modalities. The data are presented in (Table 3).

Serum zinc level in patients treated with oral zinc sulphate

The mean baseline value of serum level of zinc was 65.5±10.6 µg/dl in the patients who were assigned to receive oral zinc sulphate (220 mg twice daily, group1). The level of zinc was increased to 82.4±9.8 µg/dl and to 90.3±11µg/dl at 6 and 12 weeks respectively. The differences from the baseline value at 6 and 12 weeks was statistically significant (P<0.05).

The pattern of change in serum level of zinc in patients who received the combination oral zinc sulphate and methotrexate (group 2) were similar to the pattern of change observed in patients in the first group, the mean baseline value of serum level of zinc was 61 ±15.5 µg/dl, which was also increased to 80.6±15.1 µg/dl and 92.5±19.5 µg/dl at 6 and 12 weeks respectively. Similarly, the differences from the baseline value at 6 and 12 weeks achieved statistical significance (P<0.05). In the patients who received methotrexate alone (group 3), the mean baseline serum level of zinc was 64.6 ± 13.4 µg/dl, which was 61.1±10.7 µg/dl and 67.4±11.5 µg/dl at 6 and 12 weeks respectively. The difference from the baseline value at 6 and 12 weeks was not statistically significant (P>0.05). These results are presented in (Table 4).

Table 4. Serum zinc level measured before and 6, and 12 weeks after treatments

	Serum zinc level µg/dl			
Treatments	Baseline	6 weks	12 weeks	P value
Group 1, n=17, Zinc sulphate	65.5± 10.6	82.4±9.8*	90.1±11.0*	<0.05
Group 2, n=18, Zinc sulphate+ Methotrexate	61.0±16.0	80.6±15.1*	92.5±19.1*	<0.05
Group 3, n=18, Methotrexate	64.6±1.0	61.1±10.7	67.4±11.5	NS

*significantly different (P-value < 0.05) from the corresponding baseline value

Correlation between Serum zinc levels and % reduction of PASI-Scores

Serum zinc levels were obtained from 17 patients who were treated with zinc sulphate alone and from 18 patients treated with methotrexate alone or the combination of zinc sulphate and methotrexate. In the group of patients who received zinc sulphate alone the magnitude of increase in serum zinc level was positively correlated with the % reduction from baseline values of PASI Score (r=0.50, p<0.05), (Figure 1). Similar pattern of positive and significant correlation was also found in patients who were treated with the combination of zinc sulphate and methotrexate (group 2) (r=0.76, p<0.001). While poor correlation was found in the patients who were treated with methotrexate alone (r=0.1, data not presented)

Side effects

Oral zinc sulphate was well tolerated in the range of doses used in this study (220 mg/ twice daily), minor gastric upset was reported in around 30% of patients and none was withdrawn from the study. The side effects of methotrexate was reported in 85% of patients, the majority had nausea and vomiting but in one patient thinning of the hair was reported.

DISCUSSION

Psoriasis is a common, chronic, relapsing, distressing skin disease of unknown aetiology that affects 1-3% of the population.[13] Psoriasis is thought to be an immunologically mediated disease where T-cells play an important role in its pathogenesis[14], unfortunately, there is no unique curative systemic or topical treatment.

Zinc sulphate has been used as an immunomodulator in the treatment of many dermatological problems such as cutaneons leishmaniasis[15], recalcitrant common warts,[16] Behcet's disease[17], rosacea[18], erythema nodosum leprosum[19] and alopecia areata.[20] There are reports documenting serum zinc level is lower in psoriatic in comparison to non psoriatic patients.[21,22] This has laid the basis for investigating oral zinc sulphate treatment alone or in combination with methotrexate in psoriatic patients and compare these effects with that produced by methotrexate alone.

Oral zinc sulphate achieved a good response in about 60% of patients but the onset of that action was slow. The patients started to notice improvement 8 weeks after treatment. Methotrexate alone achieved even better remission in 70% of the patients, at 6 weeks of treatment.

Methotrexate in combination with oral zinc sulphate achieved a good response in about 85% of the patients, and the effect appeared earlier and at the end of the fourth week of treatment. We have to admit that we were unable, for ethical reasons, to recruit a control group of psoriatic patients main-

tained on placebo treatment for that length of time with which comparison with active treatments can be made.

Oral zinc sulphate was not widely studied for treatment of psoriasis but in one clinical trial[8] oral zinc sulphate was evaluated in patients with chronic plaque psoriasis in doses and duration comparable to the dose and duration used in the present study. In that study, however, no clinical improvement was reported. The observed effect in the present study could be explained on the basis of testing oral zinc on different clinical type of psoriasis; severe type in this study, and genetically and environmentally different population. The observed effect of oral zinc sulphate in the present study might be due to improving low levels of serum zinc that all patients have prior to their entry to the study. Their mean serum zinc level was 63.6 ±13.1 µg/dl compared to a normal serum values of 87 ± 9 µg/dl for adult and 92.9 ± 16 µg/dl for children.[18] Low serum level of zinc could be due to exfoliation[21] from the skin of psoriatic patient or due to consumption of low zinc containing foods. It was also found in other studies that a level of zinc of 70.08±4.23 µg/dl, which is lower than normal range, was seen in psoriatic patients with a skin lesion more than 10% of body surface area.[20] In another study, a positive relationship was found between decreased zinc levels and PASI score in psoriatic patients with a lesion more than 20% of body surface area.[23] Serum zinc level was evaluated in normal healthy population and in psoriatic patients in a study performed in Baghdad, serum zinc level was found low in the normal population and was even lower in psoriatic patients.[24] An additional factor which might be involved in low serum zinc level in developing countries is the high consumption of cereal proteins that contain large quantities of phytates which bind dietary zinc and iron rendering them unavailable for absorption.[25] In the present study we found that improvement in PASI score was associated with zinc supplementation that increases serum zinc level. These results further support the use of oral zinc in the treatment of psoriasis particularly in those patients who are zinc deficient from the start.

Although methotrexate alone induced marked remission in about two third of the cases but as a cytotoxic drug unacceptable side effects are anticipated, the most annoying is liver toxicity.[26] Methotrexate at therapeutic doses in combination with oral zinc sulphate achieved even better remission.

Although the mechanism(s) by which zinc produces effect is not well understood, however, the followings are possible mechanisms: immunomodulation[27], antiproliferative mechanism which may involve the regulation of DNA transcription factors[28], and antioxidant protective effect[29], as many studies showed that superoxide dismutase (SOD) was consistently higher in lesional psoriatic skin as compared to uninvolved skin.[29,30]

In conclusion, Zinc sulphate was well tolerated and found effective in the treatment of psoriasis. The effect of combination with zinc sulphate and methotrexate was better than methotrexate or zinc sulphate alone. Such combination in modified doses can be used to maintain acceptable therapeutic response with minimal side effects. Further studies are needed to make clearer the effectiveness of different treatment modalities in Psoriasis.

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