

Oral Zinc Sulphate in Treatment of Alopecia Areata (Double Blind; Cross-Over Study)

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Abstract

Background: Alopecia areata is a common autoimmune disease that encountered world-wide. Many modalities have been used but no one was universally effective. Zinc sulphate has been used in the treatment of many skin diseases.

Objective: To establish the effectiveness of oral zinc sulphate in the treatment of patchy alopecia areata

Patients and Methods: Patients with alopecia areata who attended the Department of Dermatology-Baghdad Teaching Hospital was recruited into randomized, placebo-controlled, double-blind cross-over trial between February 2008 and September 2009. Patients were randomly allocated to receive either zinc sulphate 5mg /kg/day in three divided doses (Group A) or identical placebo capsules (Group B). Zinc sulphate and placebo capsules were given in a double-blind manner, following 3 months of starting the treatment, the patients crossed over, i.e. patients on zinc sulphate shifted to placebo and vice versa.

Results: One hundred patients (60 males and 40 females) with patchy AA met the inclusion criteria and enrolled for the study. Sixty-seven patients completed the study, 41(61%) males and 26 (39%) females, their ages ranged from 1.6 - 68 (22.031 ± 14.8505) years. Duration of the disease ranged from 1 - 48 (14.4 ± 14.8875) weeks. In group A, at the end of third month, complete hair re-growth with terminal hairs have been obtained in 22 (59.45%) patients. After shifting to placebo treatment the hair continued to grow without relapse and at the end of sixth month, the complete hair re-growth was occurred in 23(62.16%) patients. In group B, at the end of third month, complete hair re-growth had been obtained in 3 (10%) patients. While, after shifting to zinc sulphate the complete hair re-growth obtained in 20 (66.67%) patients. No important side effects were reported apart from mild gastric upset in 8 (11.9%) patients.

Conclusion: Oral zinc sulphate is one of the effective treatment options for AA with low relapse rate after stopping of the treatment.

Keywords: Alopecia Areata; Zinc Sulphate

Introduction

Alopecia areata (AA) is an organ-specific autoimmune disease that involves the hair follicles and sometimes the nails [1], that is characterized by rapid and complete or nearly complete loss of hair in one or more round or oval nonscarring patches that can affect any hair bearing area [2-3].

Many medications have been used in its treatment including topical, intralesional and systemic corticosteroids [1,4,5], topical irritants [6], topical minoxidil [7], PUVA [8] and others. However, for many patients, therapy is limited by poor efficacy and/or problems with toxicity. Zinc sulphate had been used in the treatment of many skin diseases such as cutaneous leishmaniasis [9], recalcitrant viral warts [10], Behcet's disease [11] and rosacea [12], perifolliculitis capitis abscedens et suffodiens [13], recurrent aphthous stomatitis [14].

So, this study was designed to establish the effectiveness of oral zinc sulphate in the treatment of patchy alopecia areata.

Patients and Methods

This is a randomized, placebo-controlled, double-blind cross-over trial of oral zinc sulphate in the treatment of AA [15].

Patients with AA, who attended the Department of Dermatology - Baghdad Teaching Hospital, Baghdad, Iraq, were recruited into this study from February 2008 to September 2009. Patients who included in the trial comprised those with patchy AA of up to one year duration. While alopecia totalis, universalis, ophiasis, sisaipho, Down's syndrome

with AA, diabetic patients were excluded from the study. All cases were received no treatment for at least 2 months before starting therapy.

The nature of this trial was explained to each patient and formal consent was taken before the start the therapy, after full explanation about the nature of the disease, course, the procedure of treatment, follow up, prognosis and the need for pre and post treatment photographs. Also, the ethical approval was performed by the scientific committee of the Scientific Council of Dermatology & Venereology-Iraqi Board for Medical Specializations.

Physical examination was performed for each patient considering the following: site, number, exclamation's mark hair, color of the hair, nail changes. Serum zinc level was estimated in all patients at the beginning of the trial, as a base line, after 3 months and after 6 months. ZnSO₄ powder, (from MERK, France), was mixed up with glucose

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powder, as an excipient, by away was called geometrical mathematical method. Identical capsules which were filled up with glucose powder alone were used as a placebo.

Patients were randomly allocated to receive either zinc sulphate capsules in a dose of 5 mg/kg/day in three divided doses as group A, or identical placebo capsules, three times daily as group B. Patients were instructed to take the drug after meals. After 3 months of starting treatment, the patients were crossed over i.e. patients on placebo shifted to zinc sulphate and those on zinc sulphate shifted to placebo [15]. For young children, their parents were instructed to open the capsule and dissolve the contents in water.

Patients were followed up for 6 months. They were observed every month. Patients were evaluated clinically by looking for any hair regrowth, which was categorized into three grades:

Grade 0

no hair regrowth.

Grade I

Partial hair regrowth with villous hair (fine, thin, short).

Grade II

Complete hair regrowth with terminal hair (coarse, pigmented, and long).

During each visit of follow up, any adverse effects were recorded.

Statistical analyses were done by using Chi-square test to compare the response to therapy in the two groups. ANOVA test was used to compare the differences among means.

Results

One-hundred patients were included in the study; 60 (60%) males and 40 (40%) females; male to female ratio was 1.5/1. Thirty-three patients were defaulted from the study; thirteen patients were from group (A), while twenty patients were from group (B) for unknown reason. Sixty-seven patients completed the study, 41 (61%) males and 26 (39%) females. Their ages ranged from 1.6 - 68 years with a mean \pm SD of 22.031 \pm 14.8505 years. The duration ranged from 1 - 48 weeks with a mean \pm SD of 14.4 \pm 14.8875 weeks. Personal history of AA was observed in 23 (34%) patients while family history of AA was observed in 10 (14.9%) patients. The number of patients who

experienced emotional distress was 41 (61%). BCG vaccinated patients were 48 (71%). Personal history of atopy was presented in 28 (41%) patients while family history of atopy was found in 10 (14.9%) patients. Personal history of autoimmune diseases, (vitiligo and thyroiditis), was presented in 6 (8.9%) patients while family history of autoimmune diseases, (vitiligo, thyroiditis and diabetes mellitus), was found in 22 (32.8%) patients. The color of the hairs was black in 30 (44.7%) patients while it was brown in 35 (52.2%) patients and it was white in 2 (2.9%). Exclamation mark hairs were observed in 49 (73%) patients. Scalp was the commonest site to be involved, 56 (83.5%) patients, beard area was involved in 12 (17.9%) patients, and eye brows in 6 (8.9%) patients while the eye lashes in 2 (2.9%) patients. The number of patches ranged from 1 - 11 with a mean \pm SD of 2.51 \pm 2.04245 lesions. Nail changes were seen in 32 (47.7%) patients, pitting was the commonest finding, 21 (31%) patients then ridging 19 (28%) patients and 1 (1.49%) patient was having onychoschizia. The response to treatment was not statistically significant among the patients in regard to the duration of AA, age, gender, atopic diathesis, nail involvement and presence of autoimmune diseases.

Group (A)

The total number of patients who completed the study was 37 patients. The mean duration of the disease was 14.7 \pm 27.32weeks. At the end of 3rd month, 22 (59.45%) patients achieved grade II, 5 (13.51%) patients achieved grade I and 10 (27.02%) patients achieved grade 0 (Table 1). The growth of hair was almost equal in all patches in each patient.

After shifting to placebo treatment, the patients who developed hair growth during the first 3 months continued to maintain their hair with an additional 2 patients showed hair growth at the end of 5th month, one with terminal and other with partial hair growth and the results at 4th, 5th and 6th months were shown in (Table 1). When we compared between 3rd and 6th months at the same group (A) (after crossing over) regarding the patients who developed complete hair growth, the P value=0.8118 (statistically non significant). χ^2 (Yate corrected)= 0.0567. The serum zinc levels, before treatment, were within the normal range with a mean \pm SD of 100.2162 \pm 16.0168 that increased after 3 months of treatment with zinc sulphate with a mean \pm SD of 114.3783 \pm 7.0710 then decreased after shifting to placebo but remained above the base line level (before treatment), 107.4864 \pm 6.3639. (ANOVA test, P value < 0.0001.

Type of response	Treatment with zinc sulphate						Treatment with placebo					
	After 1 month		After 2 months		After 3 months		After 4 months		After 5 months		After 6 months	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Grade 0	21	56.76	13	35.14	10	27.02	10	27.02	8	21.62	8	21.62
Grade I	9	24.33	8	21.62	5	13.51	5	13.51	6	16.21	6	16.21
Grade II	7	18.91	16	43.24	22	59.45	22	59.45	23	62.16	23	62.16
Total	37	100	37	100	37	100	37	100	37	100	37	100

Table 1: The results to treatment in group (A), who started with zinc sulphate.

Type of response	Treatment with placebo						Treatment with zinc sulphate					
	After 1 month		After 2 months		After 3 months		After 4 months		After 5 months		After 6 months	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Grade 0	28	93.3	26	86.7	24	80	12	40	8	26.66	4	13.33
Grade I	0	0.00	1	3.3	3	10	9	30	5	16.66	6	20
Grade II	2	6.7	3	10	3	10	9	30	17	56.66	20	66.67
Total	30	100	30	100	30	100	30	100	30	100	30	100

Table 2: The results to treatment in group (B), who started with placebo.

Group (B)

The total number of patients who completed the study was 30 patients, while the mean duration of AA was 14.1 ± 61.43 weeks. At the end of 3rd month, only 3 (10%) patients achieved grade II. After shifting to zinc sulphate, at the last 3 months (4th-6th), there was significant increase in the number of patients who gained grade II, the P value < 0.0001 , χ^2 (Yate corrected) = 18, and at the end of 6th month, 20 (66.67%) patients achieved grade II. (The results at 4th and 5th months were shown in (Table 2). No relapse or new lesions were noticed during this period. The serum zinc levels before treatment were within the normal range with a mean \pm SD of 101.1666 ± 13.6896 that slightly increased after 3 months of treatment with placebo with a mean \pm SD of 101.5666 ± 12.3865 . P value = 0.4530, then increased after shifting to zinc sulphate but remain within the normal range with a mean \pm SD of 115.2 ± 6.8551 which was statistically significant. ANOVA test, P value < 0.0001 . The growth of hair was almost equal in all patches in each patient.

When the two groups were compared with each other, regarding the response to therapy with complete hair re-growth with terminal hair, after 3 months of treatment the difference was statistically extremely significant, the P value < 0.0001 and χ^2 (Yate corrected) = 15.276.

No important side effects were reported apart from mild gastric upset in 8 (11.9%) patients only, which did not need to stop the treatment.

Discussion

Alopecia areata is an organ-specific autoimmune disease [1], which occurs in genetically predisposed patients that leads to an autoimmune response against the hair follicles [15] and sometimes the nails [16], which might be triggered by interaction with environmental factors [1,17]. All of the currently available treatments for AA have a high failure rate and none is uniformly satisfactory therapy [1]. Zinc sulphate has been used as an immunomodulator in the treatment of many dermatological problems such as cutaneous leishmaniasis [9], rosacea [12], Behcet's disease [11], perifolliculitis capitis abscedens et suffodiens [13], recalcitrant viral warts [10] and others and proved to be safe, effective and lacking side effects. Oral zinc is often employed for treating hair loss, even in the absence of zinc deficiency [18]. Certain reports found that zinc deficiency may play a role in the pathogenesis of AA [19], and lower serum level of zinc was found in patients with AA [2, 19, 20], the decreased levels of zinc were seen more in those patients with prolonged duration, extensive lesions, and lesions resistant to treatment [2]. Since mid 1970s of 20th century, oral zinc sulphate was tried in the treatment of AA with variable results ranged from no significant response to 80% [21-23]. Accordingly, zinc sulphate has been used in this study as a systemic treatment for patchy AA.

In the present work, the serum zinc levels were within the normal range that increased significantly after 3 months of treatment with zinc sulphate but sustained its normal range. This was because of most of the cases of AA were of short duration and no severe case was included in the study.

The present study showed that oral zinc sulphate in a dose of 5 mg/Kg/day in three divided doses achieved good response with complete hair growth become statistically significant two months after starting therapy (43.24%), $P=0.0063$ and increased up to (59.45%), ($P < 0.0001$), at the end of the 3rd month of treatment with zinc sulphate and these values increased slightly after shifting to placebo (62.16%). The continued good response of oral zinc sulphate during placebo therapy

could be attributed to the sustained immunological action of zinc that might persist for several months or the relapse rate after therapy with zinc sulphate is markedly low. The results of the present work were comparable to other systemic modalities like, Corticosteroids [5], BCG [24], Phototherapy [1,8], Sulfasalazine [25] and Methotrexate [26]. The study also showed that oral zinc sulphate was an effective drug in the treatment of patchy AA with no significant side effects apart from mild gastric upset (Figure 1A and 1B).

So, the possible mechanism of action of zinc sulphate on the growth of hair of AA

Zinc may impact hair biology via its long-recognized, potent and immunomodulatory effects [27,28]. It exerts an indirect antioxidant action by induction of some substances that serve as the ultimate antioxidant; these substances are "metallothionein" [29]. Zinc is an essential cofactor for over 300 enzymes [zinc metalloenzymes], many of which (e.g. alkaline phosphatase, dopachrome tautomerase, metallothionein and metalloproteases) exert important functional activities in the hair follicle [30]. It is a potent inhibitor of endonucleases, the key constituents of the apoptotic machine. Given the crucial role of keratinocytes apoptosis in hair follicle regression during the involution phase of the hair cycle [catagen], zinc-mediated inhibition of endonuclease activity is a strong candidate for an inhibitor of hair follicle regression [31]. It also inhibits the expression or activity of several enzymes important in hair biology (e.g. tyrosinase, the rate-limiting enzyme of hair follicle melanogenesis) [32]. It is important for DNA stability and repair-parameters of evident importance in hair biology, since the epithelial hair matrix is one of the most rapidly



Figure 1A: Male patient with patchy alopecia areata before treatment with oral zinc sulphate.



Figure 1B: Male patient with patchy alopecia areata after 3 months of treatment with oral zinc sulphate.

proliferating and most damage-sensitive tissues in the mammalian organism [33].

In conclusion, oral zinc sulphate is an effective drug in the treatment of patchy AA working through many mechanisms mainly the immunomodulatory and antioxidant effects, with no relapse after 3 months of stopping of the treatment.

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