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THE EFFICACY OF ORAL ZINC SULFATE IN PATIENTS OF PATCHY ALOPECIA AREATA PRESENTING IN A TERTIARY CARE HOSPITAL

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ABSTRACT

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. Zinc supplement is popular trace element gave for hair loss. The objective is to estimate the efficacy of oral zinc sulfate in patients of patchy alopecia areata presenting in a tertiary care hospital. Study Randomized controlled trail study design was employed. Study was conducted at Dermatology Department Unit-II, Mayo Hospital, Lahore. Total 60 clinically diagnosed cases of patchy alopecia areata of scalp as non scarring alopecia for less than one year duration were included in the study. Patients were divided into two groups A & B by draw box methods, 30 patients in each group. In group A, oral zinc was given in the form of zinc sulfate capsules in a dose of 5 mg/kg/day in a single or two divided doses according to weight of the patient. In group B, patients received placebo in the form of brown sugar capsules once a day. Patients were followed on monthly basis till recovery or maximum upto four months. The response was assessed according to SALT score (annexure 1).10,11 Photographs were taken on each visit. All the above information was collected through a predesigned proforma. The data was entered and analyzed by using SPSS version 12.0. Mean of patients in Group-A and in Group-B was 33.23±7.03 and 33.00±7.55 years. In Group-A mean Salt score before and after treatment was 7.53±4.79 and 3.26±4.32. While in Group-B mean Salt score before and after treatment was 6.05±4.34 and 5.46±4.98. Improvement was defined as 50% or more reduction in SALT score. As per this criteria in Group-A there were 20(66.7%) patients who had improvement while in Group-B only 2(6.7%) patients had improvement. According to p-value improvement was significantly associated with treatment groups. i.e. (p-value=0.000) Improvement rate of Group-A was high as compared to that of Group-B. Among male and female patients significant improvement was seen in Group-A patients. i.e. [p-value (male)=0.000 & p-value (female)=0.013] Based on these results it can be said that oral Zinc therapy had a positive and significant role in treating patients with patchy alopecia areata. In terms of SALT scoring system improvement (>50% reduction in SALT score.) was seen in 66.7% patients who were treated with oral zinc.

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1. INTRODUCTION

Many treatment modalities have been used for its treatment including topical and systemic corticosteroids, minoxidil, phototherapy, dithranol, contact immunotherapy and others.[1]Oral zinc is used in various dermatological disorders such as cutaneous leishmaniasis, recalcitrant viralwarts, recurrent aphthous stomatitis, Bechet's disease, rosacea and perifolliculitis abscedens et suffodiens.[8] Sharique et al used zinc sulfate in alopecia areata in 100 patients and found it successful in about 60 % of cases in comparison to 10% response with placebo.[8]Alopecia areata has a devastating impact on physical, social and psychological life of an individual.[9] There is no time tested treatment available for alopecia areata up till now,[10]therefore research for new therapeutic modalities is need of the time and zinc sulfate is one of the emerging treatment. There is no such study in this part of the world so far and this study will provide an insight for the role of zinc sulfate in alopecia areata in this region.

2. REVIEW OF LITERATURE

2.1 Dynamic of hair loss

Hair follicle growth occurs in cycles. Each cycle consists of a long growing phase (anagen), a short transitional phase (catagen) and a short resting phase (telogen). At the end of the resting phase, the hair falls out (exogen) and a new hair starts growing in the follicle beginning the cycle again. There are considerable variations in the length of the three phases, with the duration of the anagen determining the type of hair produced, particularly its length. Normally about 100 strands of hair reach

the end of their resting phase each day and fallout.[13] Hair loss in non scarring alopecias, including alopecia areata essentially represents a disorder of hair follicle cycling [14]. It is believed that in AA, an as yet unidentified trigger stimulates an autoimmune lymphocytic attack on the hair bulb. This inflammation is specific for anagen hairs and causes anagen arrest. A disruption of the growing phase, that is anagen arrest, causes abnormal loss of anagen hairs (anagen effluvium), clinically recognized as dystrophic anagen hair with tapered proximal ends and lack of root sheaths. A related but distinct entity observed very frequently in women is 'telogen effluvium'. This is an umbrella term inclusive of conditions wherein the affected hairs undergo an abrupt conversion from anagen to telogen (anagen release), clinically seen as localized shedding of hair in the telogen and morphologically identified as hair with a depigmented bulb [15].

2.2 Epidemiology & demography

Of note, diagnoses of AA in prepubescent individuals seems to indicate poor prognosis [19, 23]. The epidemiology of AA also reflects the contribution of heredity factors. Of the 0.1% of the human population that developed AA, 10% to 42% reported a positive family history of AA, usually involving at least one first-degree relative [18, 24]. The age of onset of AA also reflects familial history, with nearly 40% of cases having a positive familial history if diagnosed before age 30, but only about 7% if onset occurred later on in life [24]. Twin studies tend to show a concordance rate of about 55% [24], implicating the contribution of heredity factors in AA.

2.3 Autoimmunity

Clinical evidence favoring autoimmunity suggests that alopecia areata is associated with other autoimmune conditions, the most significant of which are thyroid diseases and vitiligo. For instance, in a retrospective cross-sectional review of 2115 patients with alopecia areata who presented to academic medical centers in Boston over an 11-year period, comorbid autoimmune diagnoses included thyroid disease (14.6%), diabetes mellitus (11.1%), inflammatory bowel disease (6.3%), systemic lupus erythematosus (4.3%), rheumatoid arthritis(3.9%), and psoriasis and psoriatic arthritis (2.0%). Other comorbid conditions found included atopy (allergic rhinitis, asthma, and/or eczema; 38.2%), contact dermatitis and other eczema (35.9%), mental health problems (depression or anxiety; 25.5%), hyperlipidemia (24.5%), hypertension (21.9%), and GERD (17.3%)[26]. In conclusion, the beneficial effect of T-cell subtype depletion on hair growth, the detection of autoantibodies, the ability to transfer alopecia areata from affected animals to non-affected animals, and the induction of remission by grafting affected areas onto immunosuppressed animals are evidence in favor of an autoimmune phenomenon. Certain factors within the hair follicles, and possibly in the surrounding milieu, trigger an autoimmune reaction. Some evidence suggests a melanocytic target within the hair follicle. Adding or subtracting immunologic factors profoundly modifies the outcome of hair growth. [26]

2.4 Genetics

Many factors favor a genetic predisposition for alopecia areata. The frequency of positive family history for alopecia areata in affected patients has been estimated to be 10-20% compared with 1.7% in control subjects[27]. The incidence is higher in patients with more severe disease (16-18%) compared with patients with localized alopecia areata (7-13%). Reports of alopecia areata occurring in twins also are of interest. No correlation has been found between the degree of involvement of alopecia areata and the type of alopecia areata seen in relatives. Several genes have been studied and a large amount of research has focused on human leukocyte antigen. Two studies demonstrated that human leukocyte antigen DQ3 (DQB1*03) was found in more than 80% of patients with alopecia areata, which suggests that it can be a marker for general susceptibility to alopecia areata. The studies also found that human leukocyte antigen DQ7 (DQB1*0301) and human leukocyte antigen DR4 (DRB1*0401) were present significantly more in patients with alopecia totalis and alopecia universalis.[28]

2.5 Innervation and vasculature

Another area of interest concerns the modification of perifollicular nerves. The fact that patients with alopecia areata occasionally report itching or pain on affected areas raises the possibility of alterations in the peripheral nervous system. Circulating levels of the neuropeptide calcitonin gene-related peptide (CGRP) were decreased in 3 patients with alopecia areata compared with control subjects. CGRP has multiple effects on the immune system, including chemotaxis and inhibition of Langerhans cell antigen presentation and inhibition of mitogen-stimulated T-lymphocyte proliferation. [29] CGRP also increases vasodilatation and endothelial proliferation. Similar findings were reported in another study, in which decreased cutaneous levels of substance P and of CGRP but not of vasoactive intestinal polypeptide were found in scalp biopsy specimens. The study also noted a lower basal blood flow and greater vasodilatation following intradermal CGRP injection in patients with alopecia areata compared with control subjects. More studies are needed to shed light on the significance of these findings. [29]

2.6 Stress

CRH-R2 is a major receptor in dermal compartments and its aberrant expression could contribute to the local HPA axis and response to inflammation [44, 46]. Estrogen receptor 1 (esr1)expression was also elevated in AA-affected mouse hair follicles and esr1 is known to regulate the HPA response to stress [44]. This suggests that the observed changes to the local skin HPA and the aberrant central HPA activity are a consequence of the immune system activity in AA and may be expressed as an inability to cope with stress. The evidence that stress can modulate AA is less clear, but the functional data thus far suggests it is possible. CRH can induce mast cell differentiation from hair follicle mesenchyme [47] and the above suggests CRH/receptor activity is high in AA skin. Differences in neuropeptide substance P expression occur with AA development [48, 49]. Applying substance P to the skin of AA-affected mice induces mast cell degranulation, accelerates hair follicle catagen regression, and increases numbers of CD8+T cells-expressing granzyme B[50]. These and other data suggest that there is a feedback loop; inflammatory activity in AA can modify the HPA axis and stress responses, but inturn, increased HPA activity may accentuate inflammatory activity. Whether the effect is enough to actually induce AA onset remains to be proven. [50]

2.7 Diet

In studies on AA development in populations in different geographical settings, the lifetime risk of AA in the United Kingdom and the United States is 1.7% [30],whereas the lifetime risk in Japan has been estimated at less than 1% [31]. However, it has been observed that the Japanese population living in Hawaii, where a Westernized non-soy diet predominates, has disproportionally higher AA incidence [55]. Whether these observational studies done on human populations truly reflect a significant difference in environmental or dietary influence remains to be seen.

2.8 Classic forms

A - Alopecia areata in single or unifocal plaqueIn this form there is a single, round or oval, smooth alopecic plaque, in which the skin coloration is normal, with hair of a normal appearance in the periphery of the plaque that is easilyplucked by traction (demonstrating activity of theprocess) typical exclamation mark hair can be present.

B - Alopecia areata in multiple or multifocal plaques in this form typical alopecic plaques occur thataffect the scalp or other pilar areas.

C - Ophiasic alopecia areata

In this presentation, the hair loss occurs alongthe line of temporo-occipital implantation, giving riseto an extensive alopecic area, in a band that reachesthe inferior margins of the scalp.

D - Alopecia totalis

There is total loss of terminal hair of the scalpwithout affecting other body hair, there can also beungual involvement.

E - Alopecia universalis

There is total loss of body hair, involving thescalp, eyelashes, eyebrows, beard and mustache,armpits and genital areas. In general, it occurs in association with a variety of ungual lesions. Besides these forms that are considered classic,there are atypical presentations of alopecia areata:[60]

2.9 Atypical forms

A - Sisaifo type alopecia areata (inverse ophiasis)

In this form, the hair loss involves the entirescalp except for the lower margins, along the line oftemporo-occipital implantation. It is the inverse clinical image of the ophiasis form.

B - Reticular alopecia areata

In this form, multiple alopecic plaques occur separated by narrow bands of preserved hair, conferring areticulated aspect to the picture.

C - Diffuse alopecia areata

In this form, the hair loss is acute and widespread. It can be the initial form, mainly among children and adolescents, or can develop from plaqueforms. Most of these cases develop into the more serious alopecia totalis or universalis forms. It is the mostdifficult form to diagnose, demanding a differentialdiagnosis with acute telogen deffluvium, androgenetic alopecia and also alopecia syphilitica. Thus necessitating complementary exams in general and evenhistopathological exam by biopsy.[31, 60]

2.10 Clinical presentation

Scalp and body hair such as eyebrows, eyelashes, beard, underarm hair, and pubic hair may be affected (Alopecia Totalis), as well as the entire body (Alopecia Universalis). The ophiasis pattern refers to a severe form of AA extending along the posterior occipital and temporal scalp margins. The affected skin appears normal with no grossly evident epidermal alterations such as scaling or follicular abnormalities [63]. In all forms ‘‘exclamation point hairs’’ are found, that become narrower along the length of the strand closer to the base may be seen within or around the areas of alopecia[64]. Upon regrowth, hair often initially lack pigment resulting in blonde or white hair [65]. Nail changes can be seen in a portion of patients (10–66%) of AA. Small shallow pits (30%) up to trachyonychia (sandpaper nails; 10%) are typical, rarely other changes can also be seen. A redspotted lunula and periungual erythema have been postulated as a sign of acute nail involvement [66].

2.11 Quantitating hair loss

- Scalp biopsy:This test is done when alopecia is present, butthe diagnosis is unsure. The biopsy allows for differingbetween scarring and nonscarring forms in case there is clinical distinction is difficult. Hair samples are taken from are as of inflammation, usually around the border of the bald patch.
- Daily hair counts
- This is normally done when the pull test isnegative. It is done by counting the number of hairs lost. Thehair that should be counted are the hairs from the first morning combing or during washing. The hair is collected in a clearplastic bag for 14 days. The strands are recorded. If the haircount is >100/day, it is considered abnormal except aftershampooing, where hair counts will be up 250 and be normal.
- Trichoscopy:
- Trichoscopy is a non-invasive method of hairand scalp evaluation. The test may be performed with theuse of a hadheld dermoscope or a videodermoscope. In alopecia areata trichoscopy shows regularly distributed ‘‘yellow dots’’ (hyperkeratotic plugs), micro-eclamation mark hairs, and ‘‘black dots’’ (destroyed hairs in the hair follicle opening. Nails as described earlier, show changes in the form of pitting or trachyonychia [28]. Stigmata of organ specific autoimmunity may be present on system icexamination. [67]

2.12 Gauging severity of disease

1. Severe: Alopecia totalis or alopecia universalis.
2. Ophiasis:

- Severe form in which loss of hair occurs in the shape of a wave at the circumference of the head.

The National Alopecia Areata Foundation working committee has devised ‘‘Severity of Alopecia Tool score’’ (SALT score)Price and Gummer, 1989. Scalp is divided into four are as namely, Vertex – 40% (0.4) of scalp surface area; right profile of scalp – 18% (0.18) of scalp surface area; left profile of scalp –18% (0.18) of scalp surface area; Posterior aspect of scalp – 24% (0.24) of scalp surface area. Percentage of hair loss in any of these areas is percentage of hair loss multiplied by percent surface area of the scalp in that area. SALT score is the sum of percentage of hair loss in all above mentioned areas.

3. INVESTIGATIONS

Hair pull test, hair pluck test, dermoscopy, SALT score (severity of alopecia tool score) are useful in assessing the activity and severity of the disease. Optical coherence tomography (OCT) is a recently evaluated non-invasive technique to detect the hair shaft abnormalities in AA. Bartles *et al*. demonstrated that the cross section of hairs from an AA patch was significantly lower compared with hairs of an unaffected area by this OCT. [75] Thus, OCT may be an useful non-invasive technique to differentiate AA from other causes of patchy alopecia, such as trichotillomania. Presence of exclamatory mark hairs at periphery, positive hair pull test (>6 hairs), daily hair count (>100 hairs), hair pluck test (more telogen hairs) and dermoscopy (black dots, brokenhair, and tapering hair) suggest active disease. Severity of AA can be measured by SALT score, developed by the National Alopecia Areata Foundation working committee.[76]

4. ZINC IN HUMAN HEALTH

Zinc (Zn) is an essential nutrient for all forms of life and its importance lies in the fact that many body functions are linked to zinc containing enzymes[83]. Zn as a trace element has indispensible role in human health and diseases. It has been insufficiently recognised by a number of experts as an important public health issue, especially in developing countries. It is the most abundant intracellular metal ion found in cytosol, vesicles, organelles and in the nucleus[84]. However, even a small deficiency is a disaster to human health, so as such the number of biological functions, health implications and pharmacological targets that are emerging for zinc has evoked further interest regarding its status in human health and nutrition.[85]

4.1 Zinc therapy in dermatology

Zinc, elemental or in its various forms (salts), has been used as a therapeutic modality for centuries. Topical preparations like zinc oxide, calamine, or zinc pyrithione have been in use as photo-protecting, soothing agents or as active ingredient of antidandruff shampoos. Its use has also expanded manifoldover the years for a number of dermatological conditionsincluding infections (warts, leishmaniasis), inflammatory dermatoses (acne vulgaris, rosacea), pigmentary disorders (melasma), and neoplasias (basal cell carcinoma). Although the role of oral zinc is well-established in human zinc deficiency syndromes including acrodermatitis enteropathica, it is only in recent years that importance of zinc as a micronutrient essential for infant growth and development has been recognized. We review here various therapeutic uses of both topical and oral zinc in dermatology clinical practice.[86]

4.2 Therapeutic uses of systemic and topical zinc

- Warts (Topical, Oral)
- Cutaneous leishmaniasis (Intralesional, Oral)
- Leprosy (Oral)
- Herpes genitalis (Topical)
- Dermatophytoses (Topical)
- Bromhidrosis (Topical)
- Pityriasis versicolor (Topical)
- Acne vulgaris (Topical, Oral)
- Rosacea (Oral)
- Hidradenitis suppurativa (Oral)
- Psoriasis and psoriatic arthritis (Topical, Oral)
- Eczemas (Topical)
- Ulcers (Topical, Oral)
- Behcet’s disease and oral aphthae(Oral)
- Alopecia areata (Oral)
- Oral lichen planus (Topical)
- Xeroderma pigmentosum (Topical)
- Actinic keratoses (Topical)
- Basal cell carcinoma (Intralesional)
- Vitiligo (Oral)
- Melasma (Topical)
- Keloids (Topical)
- Antiageing (Topical).[86]

4.3 Zinc physiology and zinc deficiency states

It will be prudent to revisit the physiological aspects of zinc metabolism before discussing zinc deficiency states. Briefly, an average adult weighing 70 kg has a body zinc content of1.4–2.3 gm, the highest tissue concentration (>500μg/g dry weight) being in the prostate, seminal fluid, uveal tissue, and skin. While about half of the total body zinc is in the bones, the skin

contains nearly 6% of total body zinc. As movement of zinc across various tissues is limited and there is no storage depot, the continuous external supply of zinc is important for metabolic needs, growth, and tissue repair.[86] There commended daily allowance of zinc for an average adult male is 11 mg and the requirement increases from 8 mg/d to up to 12 mg/d in females during pregnancy and lactation. Animal foods like meat, eggs, fish, and oysters are rich in zinc. Although cereals and legumes contain moderate amount of zinc, only 20–40% of the ingested metal is absorbed. Its absorption is hampered by the presence of phytates, calcium, and phosphates while chelating agents like EDTA and animal proteins increase its absorption from gut. Zinc is mainly absorbed from proximal jejunum and distal duodenum and is perhaps facilitated by the presence of low molecular weight zinc binding ligands. It is excreted mainly through feces and in small amounts in urine and sweat. Zinc deficiency is a common problem with an estimated1/3rd of world population suffering from zinc deficiency and is highly prevalent in Southeast Asia, sub-Saharan Africa, and other developing countries[87]. Zinc deficiency can be from inadequate dietary intake and poor absorption or because of increased loss. Endemic zinc deficiency occurring in rural Iran, Egypt, and Turkey has been attributed to eating whole grain bread with high fibre and phytate contents that render zinc nearly un-absorbable. Poor-socioeconomic status, protein calorie malnutrition, protein restricted and vegetarian diets, anorexia nervosa, exclusive parenteral nutrition, chronic gastrointestinal diseases, hookworm infestation and malabsorption syndromes, pancreatic insufficiency, chronicrenal failure or malignancies, infants on formula milk with low zinc or parenteral alimentation, and a crodermatitis enteropathica are some of the predisposing factors for poor availability and/or absorption of zinc.[86]

4.4 Use of ZN in disorders of hair and mucosa

Androgenetic alopecia is a common disorder with an estimated 90% of males above the age of 20 years having some degree of frontal recession. Drugs like minoxidil and finasteride and surgical modalities like hair transplantation form the mainstay of treatment. Zinc has been found to possess antiandrogen action and it modulates 5α-reductasetype 1 and 2 activity[88]. Although it was less effective as compared to topical 5% minoxidil lotion, a considerable hairgrowth was observed with topical zinc pyrithione 1% solutionin androgenic alopecia in a randomized, investigator-blinded, parallel-group clinical study [89]. Alopecia areata is another common autoimmune disorder with numerous treatment modalities but none is being universally effective. Sharquie etal. [90] in a randomized placebo-controlled, double-blinded crossover study used zinc sulphate in a dose of 5 mg/kg/day in three divided doses for a period of six months and observeda visible clinical response in 62% of patients with alopeciaareata. However, there is overall paucity of relevant literature.

4.5 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[91, 92]. It exerts an indirect antioxidant action by induction of some substances that serve as the ultimate antioxidant; these substances are “metallothionein” [93]. 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 [93]. 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 [94]. It also inhibits the expression or activity of several enzymes important in hair biology (e.g. tyrosinase, the ratelimiting enzyme of hair follicle melanogenesis) [95]. 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 proliferating and most damage-sensitive tissues in the mammalian organism [96]

5. RESULTS

- Mean age of al 60 patients was 33.11±7.23 years. Minimum and maximum age of patients was 20 years and 50 years.*(Table-1)*
- Mean of patients in Group-A and in Group-B was 33.23±7.03 and 33.00±7.55 years. *(Table-2)*
- Gender distribution showed that there were 37 male and 23 female patients.*(Figure-1)*
- In Group-A there were 18 male and 12 female patients while in Group-B there were 19 male and 11 female patients.*(Table-3)*
- Mean duration of disease of patients in Group-A and in Group-B was 7.90±2.10 and 8.03±1.86 months. *(Table-4)*
- In Group-A mean Salt score before and after treatment was 7.53±4.79 and 3.26±4.32. While in Group-B mean Salt score before and after treatment was 6.05±4.34 and 5.46±4.98.*(Table-5)*
- Improvement was defined as 50% or more reduction in SALT score. As per this criteria in Group-A there were 20(66.7%) patients who had improvement while in Group-B only 2(6.7%) patients had improvement. According to p-value improvement was significantly associated with treatment groups. i.e. (p-value=0.000) Improvement rate of Group-A was high as compared to that of Group-B*(Table-6)*
- Improvement in both treatment groups was seen in relation to stratification of gender. Among male patient 13 patients in Group-A and 1 patient in Group-B had improvement while among female patients 7 in Group-A and only 1 female in Group-B had improvement. Among male and female patients significant improvement was seen in Group-A patients. i.e. [p-value (male)=0.000 & p-value (female)=0.013] *(Table-7)*

Table 1
Descriptive statistics for age of patients

N	60
Mean	33.11
SD	7.23
Minimum	20
Maximum	50

Group-A=Oral Zinc
Group-B=Placebo

Table 2
Age distribution of patients in treatment groups

	Group-A	Group-B
n	30	30
Mean	33.23	33.00
SD	7.03	7.55
Minimum	20	21
Maximum	50	50

Group-A=Oral Zinc
Group-B=Placebo

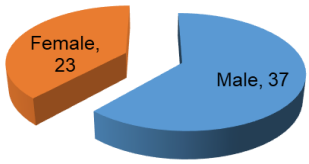

Figure 1
Gender distribution of patients

Table 3
Gender distribution of patients in treatment groups

	Group-A	Group-B
Male	18	19
Female	12	11
Total	30	30

Group-A=Oral Zinc
Group-B=Placebo

Table 4
Duration (months) of disease of patients in treatment groups

	Group-A	Group-B	Total
n	30	30	60
Mean	7.90	8.03	7.96
SD	2.10	1.86	1.97
Minimum	5	5	5
Maximum	12	12	12

Group-A=Oral Zinc
Group-B=Placebo

Table 5
Salt score in treatment groups

	Group-A		Group-B	
	Before	After	Before	After
Mean	7.53	3.26	6.05	5.46
SD	4.79	4.32	4.34	4.98
Minimum	2.20	0	1.50	0
Maximum	18	19	18	23

Group-A=Oral Zinc
Group-B=Placebo

Table 6
Improvement in treatment

		Group		Total
		Group-A	*Group-B*	
Improvement	*Yes*	20(66.7%)	2(6.7%)	22
	No	10(33.3%)	28(93.3%)	38
Total		30	30	60

Group-A=Oral Zinc
Group-B=Placebo

Note: Improvement was defines as 50% or more reduction in SALT score.
Chi-Square Test= 23.25
p-value= 0.000

Table 7
Improvement in treatment in relation to gender of patients

		Male		Female	
		Group-A	Group-B	Group-A	Group-B
Improvement	Yes	13(72.2%)	1(5.3%)	7(58.3%)	1(9.1%)
	No	5(27.8%)	18(94.7%)	5(41.7%)	10(90.9%)
Total		18	19	12	11
p-value		0.000		0.013	

Group-A=Oral Zinc
Group-B=Placebo

Table 8
Improvement in treatment in relation to age of patients

		Age Groups					
		20-30		31-40		41-50	
		Group-A	Group-B	Group-A	Group-B	Group-A	Group-B
Improvement	Yes	5(45.5%)	1(7.7%)	13(81.3%)	1(8.3%)	2(66.7%)	0(0%)
	No	6(54.5%)	12(92.3%)	3(18.8%)	11(91.7%)	1(33.3%)	5(100%)
Total		11	13	16	12	3	5
p-value		0.033		0.000		0.035	

Group-A=Oral Zinc
Group-B=Placebo

6. DISCUSSION

Many medications have been used in its treatment including topical, intralesional and systemic corticosteroids,[97, 98] topical irritants, topical minoxidil, PUVA 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, recalcitrant viral warts, Behcet's disease and rosacea, perifolliculitis capitis abscedens et suffodiens, recurrent aphthous stomatitis.[99-101] Certain reports found that zinc deficiency may play a role in the pathogenesis of AA, and lower serum level of zinc was found in patients with AA, the decreased levels of zinc were seen more in those patients with prolonged duration, extensive lesions, and lesions resistant to treatment.[97] 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%. Accordingly, zinc sulphate has been used in this study as a systemic treatment for patchy AA. The results of present study showed that oral zinc therapy showed a significant improvement in patient of patchy alopecia areata. It was observed that patients who were on oral zinc among them improvement was seen in 20(66.7%) patients while in control group improvement was seen in only 2(6.7%) patients. Improvement rate of oral zinc was high as compared to placebo. i.e. (p-value<0.05) Improvement was also compared in male (13/18: 72.2%) and female (7/12: 58.3%) patients as well which also showed that zinc therapy was effective for both male and female patients. Patients age was stratified into 3 groups and improvement was seen in them. It was observed that oral zinc showed significant improvement in all 3 age groups. i.e. [20-30 years: 5/11(45.5%), 31-40 years: 13/16(81.3%) & 41-50 years: 2/3(66.7%)]. Results of this study is consistent with the results reported by E Sharquie in his study who established the effectiveness of oral zinc sulphate in the treatment of patchy alopecia areata. As per his findings 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.[8]

Hoon Park in his study evaluated the therapeutic effects of oral zinc supplementation for twelve weeks in alopecia areata patients who had a low serum zinc. As per his findings it was observed that positive therapeutic effects were seen in 9 out of 15 patients (66.7%). Out of the 9 patients with positive therapeutic effects, 7 patients showed a marked recovery and 2 patients showed a partial recovery.[102] These results are consistent with the results of this study showing the therapeutic efficacy of zinc for treating alopecia areata. Yasmeen J. Bhat in his study assessed the levels of zinc, copper, and magnesium in the serum of AA patients. As per his findings serum zinc levels were significantly decreased (P< 0.05) in AA patients whose disease was extensive, prolonged, and resistant to treatment.[97] Zinc may impact hair biology via its long-recognized, potent and immunomodulatory effects [91, 92]. It exerts an indirect antioxidant action by induction of some substances that serve as the ultimate antioxidant; these substances are "metallothionein" [93]. 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 [93].

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 [94].Alhaj et al. demonstrated a 4-year girl with diffuse alopecia due to dietary Zinc deficiency. Her hair loss discontinued in 3 weeks after Zinc supplementation and she had no evidence of alopecia at a 4-month follow-up visit.[103] Slonim et al. showed the improvement in alopecia with oral zinc supplementation in a child with inadequate caloric intake.[104] It also inhibits the expression or activity of several enzymes important in hair biology (e.g. tyrosinase, the ratelimiting enzyme of hair follicle melanogenesis) [95]. 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 proliferating and most damage-sensitive tissues in the mammalian organism [96]

7. CONCLUSION

Oral Zinc sulphate is effective treatment modality for treating patients of patchy alopecia areata. In terms of SALT scoring system improvement (≥50% reduction in SALT score.) was seen in 66.7% patients who were treated with oral zinc. As well as it is effective for both male and female patients and in any age group of patients. Based on these results it can be said that oral Zinc therapy had a positive and significant role in treating patients with patchy alopecia areata.

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