CLINICAL EVALUATION OF ZINC THERAPY IN RHEUMATOID ARTHRITIS

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ABSTRACT

Forty-four patients who had rheumatoid arthritis were evaluated clinically and by laboratory tests. Twenty-two patients received zinc sulphate capsule (50 mg/day) plus standard treatment, while twenty-two patients received placebo and standard treatment. All th1e patients were evaluated one month later. Those who received zinc therapy revealed significant improvement in both clinical and laboratory tests, in comparison with those who received placebo therapy.

INTRODUCTION

Rheumatoid arthritis is a chronic systemic disease, usually manifested as inflammation of multiple joints. The severity of the disease varies from patient to patient, ranging from minor pain and discomfort to severe inflammation, with joint damage and deformity. Rheumatoid arthritis can also present with a number of extra-articular manifestations, including rheumatoid nodules, vasculitis, heart or lung disease, anaemia and peripheral neuropathy. Although the cause of rheumatoid arthritis is unknown. It is generally considered an autoimmune disease. It has been suggested that rheumatoid arthritis may be a manifestation of the immune response to an infectious agent[1]. Symptoms and signs of active inflammatory arthritis include *(swelling, warmth, erythema, tenderness, difficulty in making a fist, poor grip strength, and morning stiffness lasting more than 30 minutes)*. Other clinical features of active rheumatoid arthritis include, the presence of rheumatoid nodules and the evidence of vasculitis, active disease is associated with raised ESR and C-reactive protein[2]. Zinc is an essential mineral that is found in almost every cell in the body. It stimulates approximately 100 enzymes, which are substances that promote biochemical reaction in our body, it is important for a healthy immune system, and for healing cuts and wounds. Zinc is found in alpha-macroglobulin, an important protein in the body's immune system[3-6]. Zinc is part of some important antioxidant compounds, including superoxide dismutase (SOD) and zinc monomethionine. It protects the body from chemical damage, helping with detoxification of the body[7]. Zinc is an important trace element because those patients who have rheumatoid arthritis are often deficient in it. Zinc metabolism is abnormal in rheumatoid arthritis patients, which may lead to malabsorption and chronic zinc deficiency[8-10]. Neutrophils or polymorphonuclear cells are important components of human's innate phagocytic defense against pathogens and usually arrive first at sites of infection and/or inflammation[11]. Within neutrophils, the heme protein myeloperoxidase (MPO) mediates the production of hypochlorous acids (HOCl), a potent microbicidal compound[12]. Early in the phagocytic process, neutrophils undergo a respiratory burst, generating oxygen-free radicals which, after their production, decay naturally and emit light. Thus, chemiluminescence enhanced by the presence of Luminal can be used as a measure of phagocytic activity[13].

AIM OF THE STUDY

The aim of this study is to evaluate the clinical effect of zinc supplement on patients with rheumatoid arthritis and to assess the phagocytic activity of neutrophil.

SUBJECTS & METHODS

Forty-four patients, eight males and thirty-six females age ranged (24-72) years with a mean ± SD (45.5±12.1) were referred to *Al-Sader Teaching Hospital in Basrah city* between April 2002 to October 2002 and had rheumatoid arthritis according to the American criteria for rheumatoid arthritis were included[2]. Patients who had four or more of the following criteria were eligible for the study.

Morning stiffness [>1 hour]
Arthritis of three or more joints
Arthritis of hand joints
Rheumatoid nodules
Rheumatoid factor

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Radiological changes

Duration of 6 weeks or more

The proposed classification of active disease was considered when the joints involved were tender on pressure and patients experienced stress pain on passive movement associated with effusion swelling. Patients who had disease other than rheumatoid arthritis were excluded from this study. Ethical consent was obtained from the Local Ethical Committee *(Al-Sader Teaching Hospital)*. Demographic and clinical data were reported including age, sex and patient complaints, patients were also evaluated clinically and by laboratory tests. Twenty-two rheumatoid patients *(intervention group)* received zinc sulphate capsule, seventeen of them received zinc sulphate capsule *(50 mg/day)* plus standard treatment *(Sulphasalazine 500 mg t.d.s/day as a disease modifiying agents)*, the remaining five patients had received zinc sulphate capsule alone. Twenty-two of rheumatoid patients *(control group)* received placebo, twenty of them had received placebo *(glucose powder, 50 mg/day)* plus standard treatment, the remaining two patients had received placebo alone. All patients re-evaluated one month later after the supplement of zinc or placebo therapy. The evaluation includes clinical and phagocytic activity. Blood sample was taken for estimation of the following: Rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), and complete blood picture which had been analyzed before and after the therapy, in order to correlate these findings with clinical feature. The phagocytosis of neutrophil was measured by chemiluminescence technique, the reaction mixture consist of 1 ml chemiluminescence inducer, (0.1 ml of NaoH and 0.1 ml of Luminal in a 5 ml beaker, 0.01 ml of whole blood was added to the above mixture and agitated to mix well before it was poured into the measuring cuvette of photon counting system. Chemiluminescence was continuously recorded on a chart recorder, until the chemiluminescence peaked and demonstrated a definite decline[14]. The clinical and haematological evaluation include two objective indicators *(swelling and ESR)* and four subjective signs and symptoms *(morning stiffness, fatigue, joint pain and tenderness)*.

Statistical analysis was followed using Chi-squared and t-tests, P<0.05 was considered as significant.

RESULTS

Twenty-two patients *(18 females, 4 males)* who were subjected to the effect of zinc therapy had a significant clinical difference regarding the activity of the disease (P<0.001), while 22 patients who received placebo therapy showed no significant changes (P>0.05) (Table-1).

Table 1. ***The results of clinical evaluation after one-month therapy with zinc in comparison with placebo therapy.***

Activity of disease	No. (%) of patients treated with zinc sulphate		No. (%) of patients received placebo	
	At the time of presentation	*One month later*	*At the time of presentation*	*One month later*
Active	22 (100)	5 (22.7)	22 (100)	21 (95.5)
Inactive	-	17 (77.3)	-	1 (4.5)
P-value	-	P < 0.001	-	P > 0.05
Total	-	22(100)	-	22(100)

Regarding the phagocytosis as shown in (Table-2) there was a significant difference in phagocytic activity after one- month with zinc therapy plus standard treatment (P<0.001), while there were no significant changes (P>0.05) among patients who received standard treatment plus placebo.

Table 2. ***The results of phagocytosis evaluation after one-month therapy with zinc and standard treatment in comparison with placebo plus standard treatment.***

Drug	Peak height of phagocytosis (M±SD) x10^{-3}			P-value
	No.	*At the time of presentation*	*One month later*	
Standard treatment plus Zinc sulphate	17	40.6 ± 24.9	1176 ± 43.2	< 0.001
Standard treatment plus Placebo	20	52.5 ± 32.7	57.2 ± 29.6	> 0.05

Table-3, shows the phagocytosis functional activity as a compared with placebo group. Significant difference in phagocytic activity (P<0.05) was shows after one month of zinc therapy alone.

Table 3. ***The results of phagocytosis evaluation after one-month therapy with zinc alone in comparison with placebo.***

Drug	Peak height of phagocytosis (M±SD) x 10^{-3}			P-value
	No.	*At the time of presentation*	*One month later*	
Zinc sulphate alone	5	57.4 ± 18.1	95.7 ± 30.1	< 0.05
Placebo alone	2	25.0 ± 7.07	46.0 ± 28.2	> 0.05

There were no significant differences regarding the ESR level between the patients and control group.

DISCUSSION

Twenty two patients who were subjected to zinc therapy have a significant difference regarding clinical improvements (P<0.001), their joints swelling and morning stiffness were decreased associated with increase in their walking time, as well as improvement in phagocytic activity. In comparison with the other studies, a similar result was found by Simkin[15,16], but there was disagreement with other studies[17-19] which demonstrated, that zinc was not significantly more effective than placebo. The explanation for this is that rheumatoid arthritis patients are often deficient in zinc, level since zinc-dependent is an essential factor influencing the competence of cell-mediated immunity[20], low zinc intake leads to impaired status and delays healing by influencing copper status in copper-zinc superoxide dismutase activity in scavenging the oxygen free radicals generation during phagocytosis[21]. Phagocytic oxidative burst a mechanism of defense against foreign bodies leading to increase the peak height of phagocytosis invading in the inflammatory process[22], zinc may play a direct role in the maintenance of membrane structure and function by stabilizing or otherwise protecting the membrane[23], during this process zinc might be combined with copper to form superoxide dismutase, the enzyme responsible for the scavenging of harmful oxygen free radicals generated during phagocytosis activity, which is badly affect patients with rheumatoid arthritis, if not, scavenger takes its role to remove the oxygen free radicals[24].

In conclusion, zinc has a major influence on the inflammatory process which occurs in patients with rheumatoid arthritis, the enzyme superoxide dismutase which is often deficient in zinc. Zinc is also required to improve the scavenger process of oxygen free radicals generated during phagocytosis by increasing the bioavailibility of enzyme superoxide dismutase. There are no facilities for measuring titers of rheumatoid factor, neither the zinc level in the blood.

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