Topical Therapy of Xeroderma Pigmentosa with 20% Zinc Sulfate Solution

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ABSTRACT:

BACKGROUND:

Xeroderma pigmentosa although it is autosomal recessive disease but it is not uncommon problem in a certain regions in Iraq. It is always associated with well known complications of the disease like malignancies and blindness. Zinc sulfate has been successfully used in treatment of basal cell carcinoma in a form of intralesional injection & topical solution.

OBJECTIVE:

To evaluate the effectiveness of topical 20% zinc sulfate solution as a therapeutic and prophylactic agent in patients with xeroderma pigmentosa.

METHODS:

This single blind therapeutic trial was done in the Department of Dermatology & Venereology-Baghdad Teaching Hospital during the period from April 2004 to April 2005. Nineteen patients with typical features of xeroderma pigmentosa enrolled in this work. Full history and clinical examination were done for each patient regarding all points related to the disease. They were treated with topical 20% topical zinc sulfate solution and follow up was carried out for 4 months to 2 years.

RESULTS:

Nineteen patients with xeroderma pigmentosa were evaluated after treated with 20% topical zinc sulfate solution. Four patients were defaulted during follow up for unknown reason. The remaining were 15 patients (11 males and 4 females). Their ages ranged from 4-50 years with a mean± SD of 18 ±17 years. Monthly follow up showed improvement in all types of skin lesions including softening and lightening of the skin color, and clearance of solar keratosis and small malignancies. These were observed in the early course of therapy.

CONCLUSION:

This study showed that topical therapy with zinc sulfate solution had both therapeutic and prophylactic role in patients with xeroderma pigmentosa .We think that zinc sulfate is going to have a major role in management of this disease.

KEYWORDS: topical therapy, xeroderma pigmentosa, zinc sulfate.

INTRODUCTION:

Xeroderma pigmentosum is a rare autosomal recessive disease with sun sensitivity, photophobia, early onset of freckling (pigmentary changes), and premature skin aging and subsequent neoplastic changes. There is cellular hypersensitivity to ultraviolet (UV) radiation and to certain chemicals in association with abnormal DNA repair [1-6]. It is more common in Japan and Middle East, but patients were reported worldwide in all races including white Asians, blacks, Native Americans, it is relatively common in societies including Iraq ,when consanguineous marriages is common [1,3,6,7].

Approximately half of the patients with xeroderma pigmentosum have a history of acute sunburn reaction on minimal UV exposure. All patients have numerous freckles like hyperpigmentation macules[1-4,6]. The median age of onset of the cutaneous symptoms is between 1-2 years. Continuous sun exposure causes the patient skin to become dry and parchment-like with increased pigmentation [1-4,6]. The premalignant actinic keratosis developed at an early age. Patients under the age of 20 years of age have greater than 100 fold increased risk of cutaneous basal cell carcinoma, sequamous cell carcinoma or melanomas[5]. The median age of onset of non-melanoma skin cancer reported in patient with xeroderma pigmentosum was 8 years [5].

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The patients with xeroderma pigmentosum should adopt a life style to minimize UV exposure and use sunscreens with high sun protection factor (SPF) ratings (SPF 15 daily) [1,2,8-10].Cell from patients with xeroderma pigmentosum are hypersensitive to killing with UVC, UVB and UVA. Patients should be examined frequently by a family member who has been instructed in recognition of cutaneous neoplasms[1,2,8,9].

A bacterial DNA repair enzyme, den V T4 endonuclease, in a topical liposome containing preparation has been reported to reduce the frequency of new actinic keratosis and basal cell carcinoma in xeroderma pigmentosum patient in one research study [11].

Several chemoprevention strategies are potentially helpful in suppressing the occurrence of skin cancers in many diseases like xeroderma pigmentosa, epidermodysplasia verrusiformis, sold organ transplant, eruptive keratoderma, HIV/AIDS or even chronic wound or ulcers [12-14].

Such therapies may act by treating premalignant lesions such as actinic keratosis, promoting cellular differentiation, competitively inhibiting oncogenes and photocarcinogenesis. Many drugs have been used orally or topically like retinoid, 5-flurouracil, adapalen, imiquimod, photodynamic therapy, celecoxib & sunscreen [12-20]. In a recent study they used oral retinoid in treatment of skin cancers in patients with kidney transplant [13, 21, 22].

There is no effective prophylactic (preventive) and therapeutic modalities for xeroderma pigmentosum [1-2,8].

Zinc is an important essential micronutrient element for more than 300 metaloenzymes. All body tissue contains zinc and it is in the skin 5-6 times more concentrated in the epidermis than the dermis. serving as either a cofactors or an essential component of those enzymes such as alkaline phosohatase carbonic anhydrase and some dehydrogenase therefore it closely involve with protein synthesis and energy production [23].So zinc is an important antioxidant agent, protect against UV radiation, enhance wound healing, contribute to immune functions and decrease the relative risk of skin cancers[24]. Also it serves as catalyst for enzymes responsible for DNA replication, gene transcription, and RNA and protein synthesis. Also zinc augment apoptosis and in a high concentration acts as a cytotoxic agent [25-27].Apoptosis, a form of programmed cell death, is characterized by cell shrinkage and fragmentation.

Apoptosis plays a vital role in the elimination of anti-self clones, down regulation of immune responses and the killing of virally infected and malignant cells [26-30].

Furthermore, apoptosis occurs upon excessive UV light exposure, resulting in irreparable DNA damage. Mutation of p53 or over expression of bcl-2 is sufficient to enhance the formation of basal cell carcinoma by suppressing apoptosis [26,31].

Many currently used antineoplastic agents exert their therapeutic effects through the induction of apoptosis. Different cell types vary profoundly in their susceptibility, suggesting the existence of distinct cellular thresholds for apoptosis induction [32].In basal cell carcinoma, interferon–α and imiquimod induce apoptosis and is thus effective in the treatment [33].

Topical zinc ions traverse skin and can be found in dermis and blood [34], and found concentration could be increased in skin eightfold by topical application of zinc sulfate [24]. Also topical zinc sulfate or zinc chloride has been shown to protect skin of mouse against UVA and UVB induced sunburn [35]. Topical application of zinc ions has been shown to induce metalothionin, which may account for some effect [24].

Oral zinc sulfate solution has been successfully tried in the treatment of cutaneous leishmaniasis, rosacea and viral warts [29, 36, 37].Also, as (2%) intralesional mode used in cutaneous leishmaniasis, basal cell carcinoma and viral warts[26, 28, 38].

Also, topical solution (10%) and (20%) was effectively used for plane warts and basal cell carcinoma subsequently [30]. (Sharquie KE 2006 personal communication). Most recently we have tried topical solution (20%) in a number of patients with xeroderma pigmentosa, which showed its effectiveness in controlling skin lesions. These results encouraged us to conduct the present work.

The aim of the present work is to evaluate the effectiveness of topical 20% zinc sulfate solution as a therapeutic and prophylactic agent in patients with xeroderma pigmentosa and to review the literatures regarding this problem.

PATIENTS AND METHODS:

This single blind therapeutic trial was conducted in the Department of Dermatology & Venereology-Baghdad Teaching Hospital during the period from April 2004 to April 2005. Nineteen patients with typical features of xeroderma pigmentosa were enrolled in this work. A detailed history was taken from each patient or their parents regarding the following points: age,gender, address, family history, age of onset, outdoor activities, duration of the disease, drug history, and history of surgical interventions.

Thorough full clinical examination was performed for each patient to assess the distribution and extent and morphology of the skin lesions and to categorized it accordingly. Also to report eye

involvement and other organ association.

Any patient with large size(more than 1.5 cm in diameter) skin malignancy and their location near to the vital organs or need urgent surgical intervention was excluded.

All patients included in the present work had no history of treatment with topical or systemic remedies for at least two months before starting therapy.

For each patient or their parents a formal consent was taken after full explanation regarding: nature of disease, course, methods of treatment, duration , follow up and prognosis before the start the therapy. Also the ethical approval was performed by the scientific committee of the Scientific Council of Dermatology &Venereology-Iraqi Board for Medical Specializations.

A photograph was taken at the initial and subsequent visits by a mercury digital camera cyberplx S-450V at the same place and a fixed illumination.

A solution of 20% w/v zinc sulfate was prepared by dissolving 20 grams of zinc sulfate(ZnSo4 7H2O from British Drug house ,Pool, England) in 100cc of distilled water. This was applied as a topical solution twice a day and followed every month. The follow-up time was ranged from 4 months to 2 years.

RESULTS:

Nineteen patients with xeroderma pigmentosa treated with topical 20% zinc sulfate solution were evaluated. Four patients defaulted during follow up for unknown reason . The remaining were 15 patients (11 males, 4 females). Their ages ranged from 4-50 years with a mean± SD of 18±17 years while the age of onset were ranged 2-14years with a mean± SD of 1.5± 0.9 years .The family history was positive in 13(86.6%) patients only.

Sixteen(73.6%) patients had history of surgical excision of multiple basal cell carcinoma ,while 12(63.1 %) patients gave history of treatable keratoacanthoma .Also history of removing solar keratosis in 12(63.1 %) patients and sequamous cell carcinoma in 6(31.5%)cases. .

All patients had classical picture of xeroderma pigmentosa on the exposed parts of the body mainly face and neck with eye involvements. Photophobia and freckling were present in all patients(100%). On examination the skin lesions were freckling, dryness, roughness, scars of previous surgical intervention in 14(73.6%) cases,solar keratosis with small malignancies(not more than 1.5cm) as follow: basal cell carcinoma in 16(73.6%) patients, keratoacanthoma in 6((31.5%)cases, solar keratosis in 10(52.6 %) patients and sequamous cell carcinoma in 4(21.05%)cases.

Most patients received no important medical therapies apart from zinc oxide cream in some of them as sunscreen.

Monthly follow up showed improvement in all types of skin lesions including softening and lightening of the skin color, and clearance of solar keratosis and small malignancies. These were observed in the first three months of course of therapy.

Patients on longer follow up to 2 years and in continuous therapy developed no exacerbation of old lesions and no new malignancies were seen.

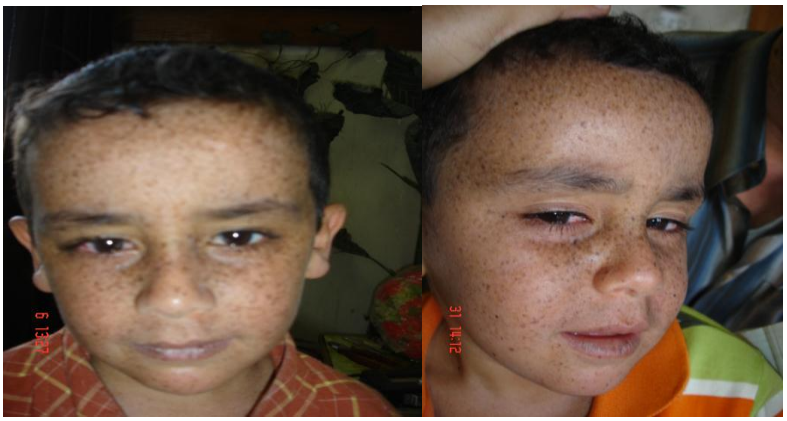

Figure 1: Showing 8 years old male patient with xeroderma pigmentosa before using 20% zinc sulfate solution.

Figure 2(a,b): Showing 8 years old male patient with xeroderma pigmentosa after 2 months of using therapy ,revealed clearance of old lesions ,no photophobia and no new lesions.

DISCUSSION:

Skin cancers are a major health problem in many countries and knowing that nearly one to five Americans will develop skin cancer in their lifetime. It is not surprising that the prevention of cutaneous malignancies through the use of oral or topical chemopreventive measures, is of significant interest to the dermatologist and their patients especially in high risk individuals like those with a history of iatrogenic, acquired or inherited immune deficiency, a genodermatosis such as xeroderma pigmentosa or Gorlin's disease, radiation exposure, chronic ulcer or wound, eruptive keratoacanthoma, leukoplakia, or a marked history of sun exposure , sun burn and solid organ transplant[12-14,21,22].

Many chemicals and drugs orally or topically have been tried in prevention and controlling skin malignancies like retinoid, 5-flurouracil, adapalen, imiquimod, photodynamic therapy, celecoxib & sunscreen re[12-22].

Xeroderma pigmentosa is a natural product of gene repair defect which is inherited as an important skin problem [1-6]; it is relatively common in societies with high blood related marriages including Iraq [1-3, 6,7].

They are often neglected and all of them practice outdoor activities, ending with a high malignancies and blindness followed by a high mortality rate. So essential measures should be taken to prevent the progression of the disease including: indoor activity, using sunscreen and taking chemopreventive chemicals and drugs [1, 2, 8-10].

Using 2% zinc sulfate solution as intralesional therapy for basal cell carcinoma has encouraged us to conduct the present work[26] .Also topical 20% zinc sulfate solution was successful therapy when preliminary study done in patients with basal cell carcinoma and solar keratosis.

The present work showed that topical zinc sulfate solution is effective in clearing and preventing the lesions in xeroderma pigmentosa patients.

The mechanism of action of zinc in xeroderma pigmentosa is not well known but probably through the following established effects of zinc : enhance wound healing, antioxidant, sunscreen, decrease cancer, protection against UV radiation, enhance DNA repair , improve immunity, accelerate apoptosis and locally might act as cytotoxic drug [23-37].

The important question to be raised is whether zinc sulfate as oral therapy or eye preparations will be effective in controlling skin and eye problems or not, so further studies and long term follow up are essentially needed.

CONCLUSION:

Topical zinc sulfate solution is a new chemopreventive agent through its therapeutic and prophylactic effects as shown to be successful in controlling skin lesions in patient with xeroderma pigmentosa. Further evaluations are strongly recommended especially with a higher concentration, to expand our experience with this drug in treatment patient suffering from xeroderma pigmentosa.

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