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Original article

Priming of Psoriasis Patients with Supplemental Folic Acid Could Minimize the Deleterious Effect of PUVA on Serum Folic Acid Levels

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Abstract

Background: Photochemotherapy is a well-established effective line of psoriasis treatment. However, folic acid deficiency was reported among psoriatic patients undergoing photochemotherapy. **Aim:** to determine the impact of PUVA on serum FA levels in psoriatic patients and if there is any role for priming by FA supplemental therapy (FAST) on this effect. **Subjects and Methods:** 62 patients with psoriasis vulgaris were included. Patients were randomly divided into two study groups, patients of FAST group received FA supplementation prior to PUVA sessions and the control group which received PUVA sessions only (didn't receive folic acid). Serum FA levels were estimated at baseline and at the end of treatment sessions using Enzyme linked immunosorbent assay technique. **Results:** post-PUVA serum FA levels were significantly decreased in comparison to pre-PUVA levels in patients of both groups, but patients of FAST group had significantly higher post-PUVA serum FA levels in comparison to that of the control group with significantly lower percentage of decrease in serum FA levels. PUVA therapy significantly reduced post-PUVA PASI score in comparison to pre- PUVA scores of patients of both groups with non-significant differences between studied groups. **Conclusion:** PUVA drastically affects serum FA. Priming of psoriasis patients for two weeks with FAST before start of PUVA could minimize this effect without affecting the outcomes of radiation therapy.

Keywords: Psoriasis; PUVA; folic acid

Introduction

Psoriasis is an inflammatory disease that affects about 2% of the population and its clinical hallmarks are sharply demarcated, erythematous plaques with thick scales (1). Psoriasis is an autoimmune chronic recurrent

inflammatory skin disorder [2] that might be due to an unbalanced ratio of Th17 cells and regulatory T cells (Treg) as evidenced by the significantly lower Treg functional ratio in patients with psoriasis in comparison to normal volunteers and by the inverse correlation between the Treg functional ratio and the Psoriasis Area and Severity Index (PASI) score [3].

Peripheral blood mononuclear cells may be involved in pathogenesis of psoriasis through a pathological process [4] that was driven by a complex cascade of inflammatory mediators [2] and acting through different expression patterns of transient receptor potential channels in immune cells [4].

Phototherapy involves repeated skin exposure to ultraviolet (UV) light that commonly used in various dermatological diseases with acceptable benefit/risk ratio, so it constitutes a highly preferable treatment modality [5]. Psoralen ultraviolet A photochemotherapy (oral or bath PUVA), as a therapeutic modality for psoriasis, depends on the interaction between psoralens, naturally occurring phototoxic compounds, and UVA to suppress DNA synthesis and cell proliferation in concomitant with induction of apoptosis of inflammatory cells [6].

Folates are a group of compounds essential during periods of rapid cell division and growth, but are not synthesized by mammals, undergo photodegradation and their deficiency is related to many diseases [7]. Folic acid (FA), a synthetic conjugated pterin derivative, is a water-soluble vitamin that is used in dietary supplementation as a source of folate [8].

Hypothesis

The current study hypothesized that pre-treatment FA supplementation may minimize the impact of PUVA on serum FA level in psoriatic patients

Objectives

Estimation of serum FA levels pre and post-PUVA exposure to determine the impact of PUVA on serum FA levels in psoriatic patients and if there is any role for patients' priming by FA supplemental therapy (FAST).

Patients and Methods

This study was a prospective interventional comparative study conducted at dermatology department of Benha University Hospitals. The protocol of the current study was approved by the Local Ethical Committee of Benha Faculty of Medicine (RC: 5-3-2021). The study was conducted since Oct 2020 till

April 2021. All patients with psoriasis vulgaris were eligible for evaluation for age, gender, body mass index (BMI) and general examination for the presence of any chronic medical problems. Then, local examination was performed for clinical diagnosis of skin problem, determination of Fitzpatrick's phototype and disease severity that was scored using PASI score, which is a quantitative rating score based on area coverage and plaque appearance into a single score ranging between 0 (no disease) and 72 (maximal disease) (9).

Exclusion criteria included pregnancy, breast-feeding, maintenance on anticonvulsants, methotrexate or folate therapy, history of allergy to phototherapy and previous exposure to phototherapy during the previous two months.

Grouping

Patients free of exclusion criteria and signed fully informed written consent were included in the study. Enrolled patients were randomly categorized into two study groups. Patients of FAST group received FA 5 mg tablet (The Nile Co. for pharmaceutical and chemical industries, Al- Ameriah, Cairo, Egypt) once daily for two weeks before starting PUVA therapy and continued throughout the treatment course and the control group which received PUVA sessions only (didn't receive folic acid).

Protocol for PUVA Therapy

Oral 8 methoxypsoralen was provided for patients of both groups in a dose of 0.6 mg/kg, 2 hours before each phototherapy session. PUVA therapy was performed using Waldmann, UVA cabin model 7002K (Herbert Waldmann GmbH & Co. KG Peter-Henlein-Straße, Villingen-Schwenningen Germany). UVA therapy was started by exposure to 0.5 J/cm^2 as an initial dose and was increased by 0.25 J/cm^2 every two sessions according to the reported cutaneous responses. Treatment sessions were scheduled twice a week for 8 weeks of treatment.

Laboratory investigations

All patients were asked to attend the Clinical Pathology outpatient lab fasting 12 hours to give blood samples. Samples were withdrawn from the anticubital vein under aseptic conditions. The collected blood samples were centrifuged at 3000rpm for 20 minutes and the supernatant was collected carefully in a clean sterile Eppindorff tube and was store at -20°C till be ELISA assayed according to the manufacturer instructions using human Folic Acid ELISA Kit (MyBiosource, Inc., Southern California, San Diego, USA; Cat. No: MBS031952) (10). Serum folic acid level was estimated before initiation of FAST and after the end of the 8-week

PUVA therapy.

Statistical analysis

Data were presented as mean, standard deviation (SD), numbers and percentages. Percentages of change in PASI score and FA serum levels were calculated as: Pre-PUVA - Post-PUVA divided by pre-PUVA value and multiplied by 100. Parametric data were analyzed using paired t-test for intra-group comparisons and One-way ANOVA test for intergroup comparisons. Non-parametric data were analyzed using Chi-square test. A p-value of <0.05 was considered significant value. Statistical analysis was conducted using IBM SPSS (Version 23, 2015; IBM, South Wacker Drive, Chicago, USA) for Windows statistical package.

Results

The study included 74 patients eligible for evaluation; 12 patients were excluded for not fulfilling inclusion criteria and 62 patients were randomly divided into the two study groups (Fig. 1). There were non-significant differences between both groups regarding demographic and clinical data (Table1).

PUVA therapy significantly reduced post-PUVA PASI score in comparison to pre-PUVA scores of patients of both groups with non-significant differences between studied groups regarding pre- and post-PUVA scores and the percentage of score decrease. Pre-PUVA serum FA levels showed non-significant differences between both groups. However, post-PUVA serum FA levels were significantly decreased in comparison to pre-PUVA levels in patients of both groups, but patients of control group had significantly lower post-PUVA serum FA levels in comparison to post- PUVA levels estimated in samples of patients of FAST group. There was significantly lower percentage of decrease in serum FA levels in patients of FAST group in comparison to the percentage of decrease in levels estimated in patients of control group (Table 2, Fig. 2). Regression analysis of patients' demographic data and pre-treatment clinical and laboratory findings and patients' priming by FAST as predictors for the extent of decrease in serum FA levels defined patients' priming by FAST as a significant predictor (β=-0.519, p<0.001) for low percentage of decreased serum FA level, while old age was defined as a significant predictor (β=0.261, p=0.017) for high percentage of decrease of serum FA after PUVA in relation to pre-treatment serum FA levels

Table (1): Demographic and clinical data of patients of both groups

Variables		Control (n=31)	FAST (n=31)	*P* value
Age (years)		37.1±15.2	37.7±12.7	0.864
Gender	**Males**	14 (45.2%)	12 (38.7%)	0.606
	Females	17 (54.8%)	19 (61.3%)	
Weight (kg)		81.8±6.2	83.5±6.4	0.281
Height (cm)		170.5±4.1	168.8±3.6	0.105
BMI (kg/m^2)	**Average (≤24.9)**	5 (16.1%)	2 (6.5%)	0.361
	Overweight (25-30)	17 (54.8%)	16 (51.6%)	
	Obese (>30)	9 (29.1%)	13 (41.9%)	
	Mean	28.2±2.9	29.4±2.8	0.116
Chronic medical problems	**No**	23 (74.1%)	20 (64.5%)	0.923
	Diabetes Mellitus	3 (9.7%)	5 (16.1%)	
	Hypertension	2 (6.5%)	2 (6.5%)	
	Chronic kidney diseases	1 (3.2%)	1 (3.2%)	
	Cardiac diseases	2 (6.5%)	3 (9.7%)	
Disease duration (years)	**<5**	14 (45.2%)	14 (45.2%)	0.445
	5-9	14 (45.2%)	10 (32.3%)	
	10-15	2 (6.4%)	7 (22.5%)	
	>15	1 (3.2%)	0	
Fitzpatrick's phototype	**Mean**	5.6±3.4	5.9±3.7	0.696
	I	13 (41.9%)	13 (41.9%)	0.451
	II	16 (51.7%)	13 (41.9%)	
	III	5 (6.4%)	5 (17.2%)	

Data are presented as mean, SD, numbers & percentages; FAST: Folic acid supplemental therapy; BMI: Body mass index; *P* value indicates the significance of intergroup differences using ANOVA test; *P*<0.05 = significant difference; *P*>0.05 = non-significant difference

Table (2): Pre- and post-treatment PASI scores and serum folic acid of patients of both groups

Variables		Control (n=31)	FAST(n=31)	*P* value
PASI score	**Pre-treatment**	4.8±2.8	5±3.5	0.806
	Post-treatment	3.2±1.9	3.3±2.2	0.816
	P value	0.010	0.025	
	% of decrease	53±16.3	49.4±19.6	0.431
Serum folic acid (ng/ml)	**Pre-treatment**	9.5±4	10.3±3.2	0.387
	Post-treatment	6.8±2.9	8.2±2.6	0.048
	***P1* value**	0.0032	0.0063	
	% of decrease	28.4±7.9	20.3±5.7	0.0002

Data are presented as mean, SD; FAST: Folic acid supplemental therapy; PASI: Psoriasis Area & Severity index; *P* value indicates the significance of intergroup differences between both groups using ANOVA test; *P1* indicates the significance of intragroup difference for pre- and post-PUVA measures using paired-t test; *P*<0.05 =significant difference; *P*>0.05 = non-significant difference

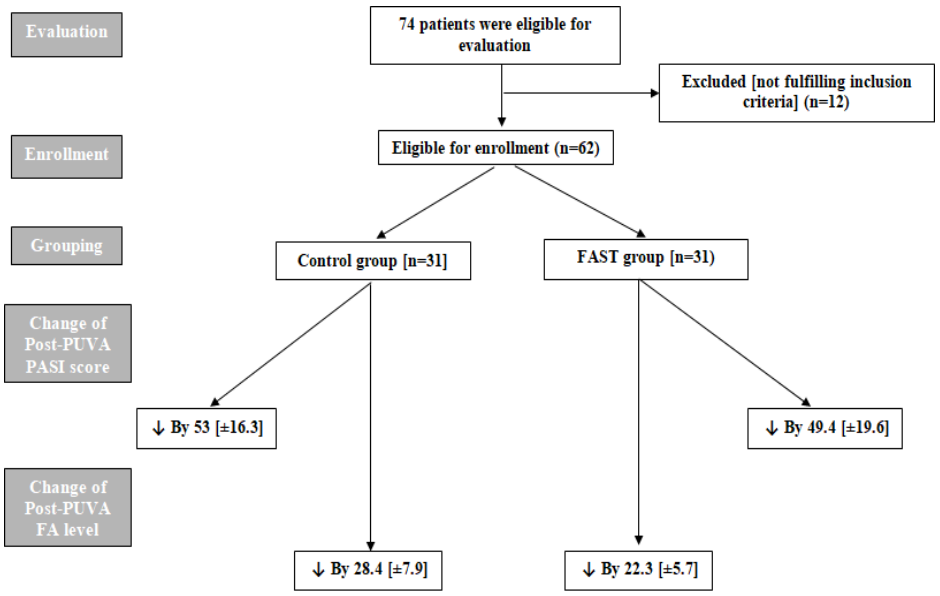

Figure 1: Percentage of decrease of PASI scores and serum folic acid levels after PUVA therapy

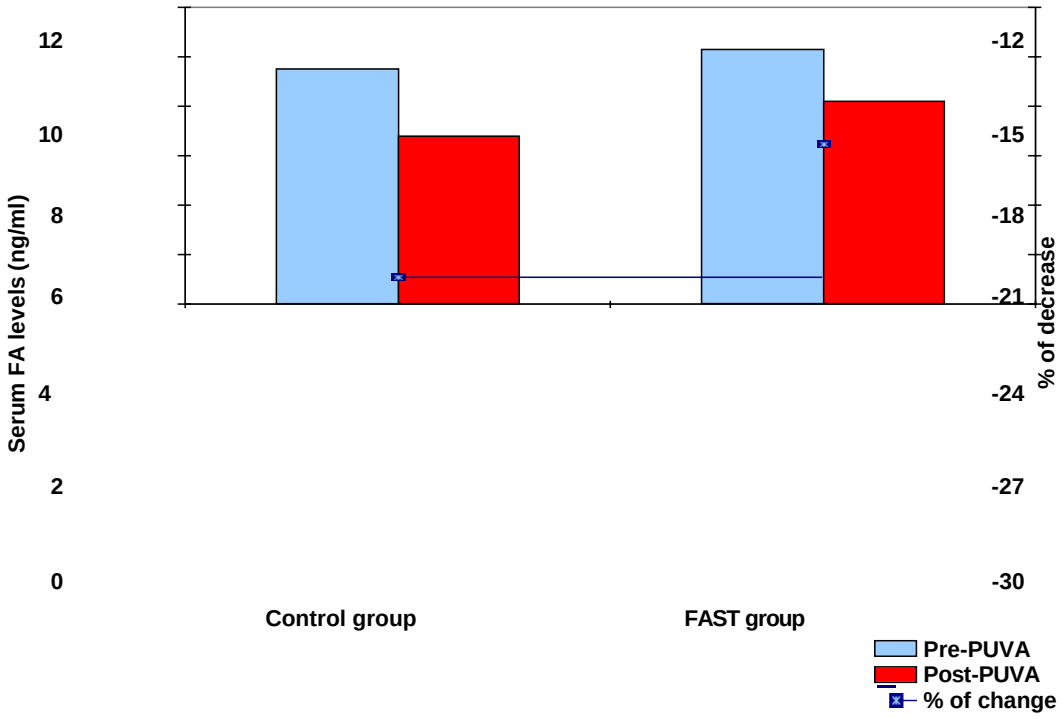

Figure 2: Mean pre- and post-PUVA serum FA levels estimated in patients of both groups

Discussion

The reported decreased serum FA levels in studied patients indicated a deleterious effect of PUVA on serum FA and this decrease was not related either to disease

severity, skin phototype, gender, or BMI.

Similarly, previous studies had reported that high cumulative narrow-band UVB (NB-UVB) doses can induce folate photo-degradation and decrease serum FA levels

in psoriatic patients [11]. Moreover, other studies have declared significant reduction of serum FA after PUVA therapy for psoriatic patients in comparison to their levels estimated before exposure, none of these patients was folate deficient[12]. The reported decrease in serum FA levels was attributed by early in vitro studies to induction of significant photolysis during in vitro exposure of serum to UV rays [13]. Recent, in vitro studies reported dramatic increase in production of H_2O_2 by UVA photosensitization when riboflavin coexisted with amino acids such as tryptophan, or with folic acid and attributed phototoxicity of UVA to skin cells to the UVA-induced oxidative stress, which accelerates the senescence of skin cells [14]. These results point to a suggestion that UVA uses folate and cellular protein constituents to induce oxidative stress in exposed cells leading to its death.

In support of this suggestion concerning the role of oxidative stress induced by PUVA, it has been proposed that slowly repaired bulky DNA damages induced by UV exposure can serve as a "molecular scar" causing reduced cell proliferation through persistent endogenous production of reactive oxygen species (ROS) as a result of mitochondrial dysfunction and activation of NADPH oxidase as evidenced by suppression of the level of ROS by combined inhibition of DNA-dependent protein kinase and Poly [ADP-ribose] polymerase 1 could suppress the level of ROS [15].

Moreover, decreased serum folate on exposure to UV is not solely character for UVA, as it was also documented for UVB, wherein it was found that NB-UVB showed dose-dependent degradation of folate with decreased serum folate levels by 19-27% [16]. These data indicated a general mechanism for UV for induction of cellular death through induction of extensive oxidative stress reactions

Application of PUVA for management of psoriasis, irrespective of disease severity, was effective therapeutic modality as evidenced by the significant reduction of PASI score after treatment in comparison to pre-treatment PASI scores. Similarly, many studies have documented that irrespective of type of phototherapy, it is an effective treatment for moderate and severe psoriasis, with improvement in

psoriatic plaques, decrease in PASI and significant reduction in histopathological changes in psoriasis after treatment [17] .

In support of the efficacy of PUVA in therapy is effective, but after 6 months, the relapse rate was higher with UVB [18]. Recently, **it was** documented that the use of medium-dose UVA1 phototherapy significantly improved the PASI score and was well tolerated by all patients and the most common side effect was skin tanning [19] .

Folic acid supplemental therapy (FAST) significantly minimized the effect of PUVA on serum FA as evidenced by the significantly lower percentage of decrease in post-treatment serum FA levels in comparison to the percentage of decrease detected in control group. This finding points to the importance of prophylactic use of FAST prior to start PUVA to maximize FA serum level so as to minimize the percentage of decrease. In line with the use of prophylactic FA therapy, **Zhang et al.,** [16] recommended all women of childbearing age on phototherapy to take 0.8 mg/day of folate supplements to reduce the risk of neural tube defects in unplanned pregnancy. Also, **Yousefkhani et al.,** [12] recommended correction of folate deficiency before PUVA therapy as it may be aggravated by phototherapy especially in fair-skinne

treating psoriasis, it was fond that compared NB-UVB versus PUVA and found 3 sessions/ week of either UV

Conclusion:

Despite the effectiveness of PUVA as a therapeutic modality for psoriasis, it drastically affects serum FA and may expose the patients to the risk of hematological disorders secondary to FA deficiency. Priming of psoriatic patients for two weeks with FAST before start of PUVA could minimize this effect without affecting the outcomes of radiation therapy.

Recommendations:

Wider scale multicenter study is mandatory to establish the obtained results. Also, studies including patients with fair skin are required to recommend the priming protocol as an established.

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