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ORIGINAL ARTICLE

Efficacy of Oral Omega-3 Fatty Acids on Uremic Pruritis in Hemodialysis Patients

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ABSTRACT

Chronic kidney disease-associated pruritus (CKD-AP) is a distressing, often overlooked condition in patients with CKD and end-stage renal disease. It remains one of the most tormenting, frequent, and potentially disabling problems in patients with an advanced or end-stage renal disease who are on dialysis including peritoneal dialysis and hemodialysis. Omega-3 fatty acids are increasingly being used for their clinical benefits some of which are relevant to individuals with advanced CKD. It was found to be a safe drug that has other benefits on uremic pruritis such as reducing cholesterol, triglycerides, LDL, blood pressure, atherosclerosis, and oxidative stress.

Patient and methods: This study was performed as a randomized, clinical trial study on 36 patients under hemodialysis three times a week, for 4 hours each session to assess the effects of Omega-3 fatty acids for treatment of pruritis in hemodialysis patients.

Conclusion: Omega-3 fatty acids was found to be a safe drug and achieved a high therapeutic response with a reasonable cost that is maintained for a relatively long period. In addition to reducing cholesterol, triglycerides, blood pressure, atherosclerosis, and oxidative stress

Keywords: pruritus; CKD; itching; Omega-3 fatty acids

INTRODUCTION

Uremic pruritis (UP), more accurately named chronic kidney disease-associated pruritis (CKD- AP), remains one of the most tormenting, frequent and potentially disabling problem in patients with advanced or end stage renal disease**) [11].** Pruritis which is an unrestricted and uncomfortable sensation that elicits the desire to scratch, has been well recognized as a common complication in patients with chronic renal failure. It influences 15 % - 49% of pre-dialysis CKD patients and 50% - 90% of those on dialysis including peritoneal dialysis and hemodialysis **[12].**

A number of different factors and mechanisms have been proposed to explain the pathogenesis of UP, but no one of these is completely convincing. At least four main hypotheses have been put forward: dermatological abnormalities, an immune-system derangement that results in a pro-inflammatory state, an imbalance of the endogenous opioidergic system, and a neuropathic mechanism **[13].**

Intensity and distribution of CKD-AP changed over time, it worse during night-time than during day-time. It is most intense during or immediately after dialysis in 25% of affected patients**.** It may be generalized or affects back, face, and arm **[2].** Primary skin lesions are not seen in patients with CKD-AP, nevertheless, linear crusts, excoriations with or without impetigo, papules or ulcerations may be observed as secondary skin lesions due to severe scratching **[14].**

Therapeutic options for CKD-AP are limited. Validity of most studies on this subject remains questionable. End stage renal disease (ESRD) patients are known to have abnormal fatty acid profiles **[3].** Thus, it seems that supplemental use of essential fatty acids and their derivatives may offer multiple health benefits to ESRD patients. Long-chain polyunsaturated omega-3 fatty acids (n-3

PUFA), which are obtained primarily from dietary sources such as cold-water fish, have diverse and potent mediating effects on the immune, inflammatory, and metabolic pathways, signal transduction, and cell membrane physiology.

Omega-3 fatty acids are increasingly being studied for their clinical benefits some of which are relevant to individuals with advanced CKD. These include, renoprotection in IgA nephropathy, maintenance of dialysis access patency and sparing of inflammation-associated muscle loss **[4].** Omega-3 fatty acids were found to be a safe drug which has other benefits on uremic pruritis such as reducing cholesterol, triglycerides, LDL, blood pressure, atherosclerosis, and oxidative stress **[9].**

AIM OF THE WORK

To assess the effects of Omega-3 fatty acids for treatment of pruritis in hemodialysis patients.

MATERIAL & METHODS

This study was carried out at the hemodialysis unit of internal medicine department, Faculty of Medicine, Zagazig University Hospitals in the period from June 2017 till December 2017. Thirty-six patients (21 men and 15 women) were enrolled in the study. The study had the approval of The Institutional Review Board (IRB) at Zagazig University.

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: Patients with end-stage renal disease of both sexes at any age who were under the intermittent hemodialysis treatment and had pruritis for over three months with no response to anti pruritic drugs.

Exclusion criteria: Patients with systemic diseases such as malignancies, hepatic cholestasis, hepatitis B and C, and the patients under steroid treatment. Also patients with hemoglobin below 10g /dl and KT /V index of less than 1.2 (Where K is the urea clearance (milliliters per minute), T, the treatment duration (in minutes), and V, the volume of urea distribution (milliliters) that is a useful guide for estimating the adequacy of dialysis therapy prescriptions). The patients under warfarin treatment and those having allergy to fish oil.

Full history was taken from each case including: Personal history (name, gender and age), Present history which included onset, course and duration of itching, time of itching and previous itching treatment (e.g. Anti-histaminic), Past history of systemic diseases (e.g. diabetes, coagulopathy etc.) and History of renal failure and dialysis.

All patients were subjected to: general examination and Dermatological examination to assess:

Skin lesion due to itching (e.g. excoriations), site of itching and associated skin lesions. The pruritus assessment has been carried out throughout the study by the same person at the start, during, and at the end of the study using detailed pruritus score (DPS) method**.** In this method, intensity, distribution, and sleep disturbance have been scored. We have assessed the patients in weekly visit at dialysis center for side effects but the pruritis score was calculated before and after consuming omega-3.

Intensity: sense of itching with no need to scratch received 1 point; few time of scratch without excoriation 2 points; frequent need to scratching 3 points; scratching with excoriation 4 points, and an itch that lead to continuous unrest 5 points. (A maximum of 10 points can be calculated during the day (5 in the morning, 5 in the afternoon).

Distribution: 1 point for pruritus in less than two areas; 2 points for pruritus in more than two areas; and 3 points for a widespread pruritus. The recorded scores for intensity and distribution were multiplied separately for morning and the afternoon. The maximum score was 30 points.

Sleep disturbance: 2 points for each wakeup because of pruritus (with a maximum of 10 points); and 1 point for each scratching with excoriation during the night (with a maximum of 5 points). Sleep disturbance and intensity-distribution scores had added up to calculate the patient's final score at the start and at the end of the study.

We calculated the mean of score among 36 patients before and after using omega 3.

Investigations including blood pressure, cholesterol, and triglycerides had been measured before and after the study. In our study, the effect of omega-3 fatty acids (fish oil) on pruritus in hemodialysis patients have been examined. The study was performed as a randomized, clinical trial on 36 patients.

Patients were under hemodialysis three times a week, for 4 hours each session and did not have the exclusion criteria. Informed consents were obtained from all patients who were included in the trial, and patients were able to leave the study if they wanted Omega-3 fatty acids have been taken as one-gram capsule every eight hours for 8 weeks 3-gram fish oil every day (omega-3 plus capsules, South Egypt drug industries co, SEDICO, 6 October City Egypt).

Patients' compliances were observed weekly and checking for the empty drug blister packs.

Before starting the project, the study had been explained to the patients and they had entered in the study voluntarily, and patients have undergone the experiment after writing consent. Considering the safety of the prescribed drug and its other benefits, its rare complications, such as dyspepsia rash, headache were explained to the patients that if they occurred, could mandate the drug to be discontinued and reported.

RESULTS

In the study:

33.3% of studied group had no previous treatment while 25.0%, 25.0% & 16.7% had anti-histaminic, anti-histaminic and emollients, and emollients respectively as shown in **(table1).** The most frequent observed skin lesion was linear crusts and excoriations (58.3%) followed by scratch marks & linear crusts (13.9%), scratch marks, linear crusts & excoriations (13.9%), linear crusts (8.3%), scratch marks & excoriations (2.8%) and scratch marks, linear crusts & papules (2.8%) as shown in **(Table 2).**

Therapeutic Response:

Thirty-six patients were enrolled in the study. Two subjects dropped out due to lack of compliance during treatment course. The response to treatment was assessed using detailed pruritus score (DPS) method devised by Dr. Duo **[8].** We have assessed patients in weekly visit at dialysis center for side effects and the pruritis score was calculated before and after the treatment. The mean blood pressure in the patients was 130 / 80 mmHg before the treatment, and 121 / 80 after the treatment that its reduction was significant. The mean triglyceride level was 123 mg / dL before receiving docosahexaenoic (omega-3) and 105 mg/ dL after the treatment, that its reduction was highly significant. The mean serum cholesterol was 147 mg / dL before the treatment and 131 mg /dL after it and the difference was not significant as shown in **(Table 3).**

In the 1st visit, the mean score was 27.4 ± 6.8; median score was 26.0 and the range of score was 17.0 – 40.0. While in the final visit the mean score was 1.2 ± 1.9; median score was 0.0 and the range of score was 0.0 – 5.0 so, there was high statistical significant decrease in score in The final visit. The score had dropped from 27.4 to 1.9 as shown in **(Table 4, Table 5).** There was no statistical significant association between studied group characteristics and occurrence of side effects as shown in **(Table 6).**94.4% of studied groups had no side effects while 5.6% only had side effects. One patient had GIT upset and abdominal distension and the other patient had GIT upset, abdominal distension and hemoptysis as shown in **(Table 7)**

Table (1): Previous itching treatment among studied group

No	12	33.3
Anti -histaminic	9	25.0
Anti -histaminic and emollients	9	25.0
Emollients	6	16.7
Total	36	100

Table (2): Skin lesion distribution among studied group**.**

Skin lesion	**N**	**%**
linear crusts	3	8.3
linear crusts and excoriations	21	58.3
Scratch marks and excoriations	1	2.8
Scratch marks, linear crusts	5	13.9
Scratch marks, linear crusts and excoriations	5	13.9
Scratch marks, linear crusts, papules	1	2.8
Total	36	100

Table (3): TC, TG and blood pressure before and after supplementation.

Variables	Pre supplementation (mean ± SD)	Post supplementation (mean ± SD)	Paired t-test	P
TC (mg/dl)	147.0 ± 29.2	131.3 ± 28.8	1.4	0.2
TG (mg/dl)	123.0 ± 34.4	105.2 ± 35.0	5.6	0.00 **
Systolic blood pressure (mmHg)	130.0 ± 30.2	121.0 ± 24.8	2.6	0.04 *
Diastolic blood pressure (mmHg)	80.0 ± 22.5	80.4 ± 15.4	1.1	0.1

** High statistical significance. * Statistical significance

Table (4): DPS Score distribution among studied group.

Score distribution	The 1st visit score	The final visit score
Mean	27.4	1.2
Median	26.0	0.0
Std. Deviation	6.8	1.9
Minimum	17.0	0.0
Maximum	40.0	5.0

Table (5): Assessment of change in DPS score among studied group**.**

Change in score	Mean	Std. Deviation	Paired t	P
The 1st visit score	27.4	6.8	23.49	0.00**
The final visit score	1.2	1.9		

** High statistical significance**.**

Table (6): Association between characteristics of studied group and occurrence of side effects.

Characteristics of studied group			Side effect		Total	X^2	P
			No	Yes			
Gender	Female	N	14	1	15	0.06	0.8
		%	41.2%	50.0%	41.7%		
	Male	N	20	1	21		
		%	58.8%	50.0%	58.3%		
Onset	Gradual	N	9	0	9	0.7	0.4
		%	26.5%	0.0%	25.0%		
	Sudden	N	25	2	27		
		%	73.5%	100.0%	75.0%		
Course	Progressive	N	18	1	19	1.26	0.53
		%	52.9%	50.0%	52.8%		
	Remission and exacerbation	N	9	0	9		
		%	26.5%	0.0%	25.0%		
	Steady	N	7	1	8		
		%	20.6%	50.0%	22.2%		
Previous itching treatment	Anti-histaminic	N	9	0	9	1.58	0.66
		%	26.5%	0.0%	25.0%		
	Anti-histaminic and	N	8	1	9		

Characteristics of			Side effect		Total	X^2	P
	emollients	%	23.5%	50.0%	25.0%		
	Emollients	N	6	0	6		
		%	17.6%	0.0%	16.7%		
	No	N	11	1	12		
		%	32.4%	50.0%	33.3%		
Skin lesion	linear crusts	N	3	0	3	1.51	0.95
		%	8.8%	0.0%	8.3%		
	linear crusts and excoriations	N	19	2	21		
		%	55.9%	100.0%	58.3%		
	Scratching and excoriations	N	1	0	1		
		%	2.9%	0.0%	2.8%		
	Scratching , linear Crusts	N	5	0	5		
		%	14.7%	0.0%	13.9%		
	Scratching , linear crusts and excoriations	N	5	0	5		
		%	14.7%	0.0%	13.9%		
	Scratching , linear crusts, papules	N	1	0	1		
		%	2.9%	0.0%	2.8%		
Total		N	34	2	36		
		%	100.0%	100.0%	100.0%		

Table (7): Side effects distribution among studied group.

Z		N	%
Side effects	GIT upset, abdominal distension	1	2.8
	GIT upset, abdominal distension & hemoptysis	1	2.8
	No	34	94.4
Overall side effects	Not side effected	34	94.4
	Side effected and discontinue	2	5.6
	Total	36	100

DISCUSSION

Uremic pruritus remains one of the most tormenting, frequent and potentially disabling problem in chronic kidney disease (CKD) patients **[11].** The underlying mechanism(s) for chronic kidney disease associated pruritis (CKD-AP) have not yet been fully understood. However, an area of substantial etiological interest with relation to uremic pruritus is the essential fatty acids deficiency and their metabolites derived from cyclooxygenase and lipoxygenase pathways including prostaglandins and leukotrienes, respectively **[5].**

In the present study, we evaluate the efficacy of omega-3 fatty acids on uremic pruritus in hemodialysis patients. The study included 36 patients with uremic pruritis who received 3 grams of omega-3 fatty acids (1 gm each 8 hours) daily for 8 weeks. Patients were evaluated for their pruritic symptoms (severity, distribution, and frequency) at the first and at the eighth week.In the final visit, comparing to the 1st visit there was high statistically significant decrease in the mean Pruritus score in the final visit. The score had dropped from 27.4 to 1.9. There was designed a prospective, randomized, double-blind, controlled study **[5]** to compare the effects of supplementation with fish oil (FO), rich in omega-3 fatty acids, with safflower oil (SO), rich in omega-6 fatty acids, on lipoxygenase activity of stimulated polymorph nuclear leukocytes and symptoms of pruritus in hemodialysis HD patients. The pruritus decreased with (FO) group more than with (SO) group in agreement with our study.Another randomized, double-blind, placebo controlled cross-over trial performed on 22 hemodialysis patients, daily oral supplementation with 3 g fish oil (containing a total of 540 mg EPA and 360 mg DHA) for 20 days significantly mitigated uremic pruritus symptoms compared with the placebo group (65%reduction in the omega-3 vs 15% reduction in the placebo group, $P < 0.001$). **[15]** Another randomized controlled trial have shown a significant improvement in pruritus symptoms in CKD patients who took omega-3 supplement compared to omega-9. **[17]** A small pilot uncontrolled study failed to demonstrate beneficial effect of omega-3 supplement on symptoms of uremic pruritus [**9].**

The study showed that there was a significant reduction of the mean blood pressure in the patients after the treatment. The mean triglyceride level showed a highly significant reduction after receiving the docosahexaenoic (omega-3), but the mean serum cholesterol level showed no significant difference after the treatment. These results were similar to findings with [**7].** Omega-3 fatty acids supplements with an average dose of 3.7 g /d and median duration of eight weeks found to be effective for decreasing the systolic blood pressures by 10 mmHg in adults with ages above 45 in a meta-analysis study **[16].** The use of omega-3 in doses of over 3-4 grams per day reduces the serum triglyceride to 25-30% of omega-3 in doses of over 3-4 grams per day reduces the serum triglyceride to 25-30%

[18]. The study showed that, 94.4% of the studied group had no side effects while 5.6% only had side effects. Half of side effected patients had GIT upset and abdominal distension and the other half had GIT upset, abdominal distension and hemoptysis which is the same finding of **[6] who** found that side effects occur in 4% of the patients in doses of 3 grams per day or above**.**Taken together, promising preliminary data on the benefits of omega-3 PUFA including relieving uremic pruritus make it an attractive treatment option that can be integrated into a CKD patient's diet. In the meantime, and considering omega-3 PUFA's multiple health benefits in other areas relevant to CKD and negligible risk profile, the current American heart association AHA omega-3 intake guidelines can wisely be applied to CKD patients suffering from symptoms of uremic pruritus. Over time, the utility and optimal dosing of omega-3 PUFA in advanced CKD patients will be elucidated via randomized clinical trials.

CONCLUSION

In conclusion, Omega-3 fatty acids were found to be a safe drug and achieved a high therapeutic response with a reasonable cost that is maintained for a relatively long period. It has other benefits on uremic patients such as reducing cholesterol, triglycerides, blood pressure, atherosclerosis, and oxidative stress. Over time, the utility and optimal dosing of omega-3 PUFA in advanced CKD patients will be elucidated via randomized clinical trials.

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