Evening primrose oil is effective in atopic dermatitis: A randomized placebo-controlled trial

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ABSTRACT

Background: Atopic dermatitis (AD) is a chronic, relapsing, itchy dermatosis of multifactorial origin, which commonly starts in childhood. Defective metabolism of essential fatty acids leading to relative dominance of pro-inflammatory prostaglandins (PGE_2 and PGF_2) has been reported as an important factor in the pathogenesis of AD. Evening primrose oil (EPO) as a source of gamma-linolenic acid (GLA) has been of interest in the management of AD. **Aim:** To evaluate the efficacy and safety of EPO in atopic dermatitis in our patients. **Methods:** Consecutive new out-patient department (OPD) patients of a referral hospital in Kolkata clinically diagnosed as having AD were randomly allocated to two groups. To the first group, evening primrose oil was supplied as 500-mg oval clear unmarked capsules, while placebo capsules identical in appearance and containing 300 mg of sunflower oil were given to the other group. Treatment continued for a period of 5 months. With pre-designed scoring system (based on four major parameters: extent, intensity, itching, and dryness), clinical evaluation was done at baseline and subsequent monthly visits. Data of the first 25 patients from each group who completed the 5 months of trial were compiled and analyzed. **Results:** At the end of the fifth month, 24 (96%) patients of EPO group and 8 (32%) patients of placebo group showed improvement. There was significant difference in outcome of treatment between two groups ($P < 0.00001$). No significant adverse effect was reported by any patient/guardian at any point of assessment. **Conclusion:** Evening primrose oil is a safe and effective medicine in management of AD. However, since not all researchers across the world have found the same good result, further large trials on Indian patients are needed.

Key Words: Atopic dermatitis, Evening primrose oil, Gamma-linolenic acid

INTRODUCTION

Atopic dermatitis (AD) is a chronically relapsing disease in the abnormally reacting skin of atopic individuals, and which is frequently associated with increased serum IgE level and a personal or family history of AD, allergic rhinitis, and/or asthma.[1] Although the etiology of AD is unknown, the disease is probably multifactorial, with interactions between genetic and environmental factors.[2] The diagnosis is mostly done on clinical grounds, and criteria proposed by Hanifin and Rajka are most widely used.[3] This disease usually begins in early life, both sexes are involved, and its prevalence has been rising steadily over the past few decades.[4] Avoidance of known precipitating or aggravating factors like extremes of temperature, excessive bathing and rubbing of skin, psychological stress, contact irritants, and aero-allergens is important in these patients. Besides this, trial with elimination diet, hydration of the skin with bath followed by application of emollients, antihistaminics, antibiotics when necessary, topical glucocorticoids, and/or tacrolimus form the first line of management of AD. Second line approaches include phototherapy, photo-chemotherapy, systemic glucocorticoids, low-dose cyclosporine, and other anti-metabolites in difficult cases. Novel approaches to treatment with potential therapeutic benefit include evening primrose oil (EPO), gamma

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interferon, thymopentin, phosphodiesterase inhibitors, extracorporeal photopheresis, Chinese herbal medicine, etc. But we are yet to find an ideal solution to this chronic dermatosis with substantial morbidity.

In 1937, low plasma levels of essential fatty acids was first reported in patients with AD.[5] Linoleic acid is the main dietary essential fatty acid (EFA). To be fully utilized by the body, it must be metabolized to a range of other substances. The first step in this pathway is delta-6-desaturation to gamma-linolenic acid (GLA), an omega-6 essential fatty acid. This step is slow and rate limiting, particularly in humans. If delta-6-desaturase is impaired for any reason, as in patients of atopic dermatitis, the supply of further metabolites may be inadequate for normal function.[6] As a consequence of impaired formation of GLA, endogenous production of prostaglandin E_1 (PGE_1) diminishes in atopic patients, leading to immune dysregulation and dominance of pro-inflammatory prostaglandins (PGE_2 and PGF_2), eventuating in dermatitis. Evening primrose oil is a natural source of linoleic acid and GLA in relatively high concentration. Other rich natural sources of GLA are plant oils like borage seed oil, black currant seed oil, hempseed oil, and spirulina (a cyanobacterium). Evening primrose (*Oenothera biennis*) is a little plant with pretty yellow flowers blooming in the evening, related to rosebay willow herb family. It is nowadays grown as a cash crop, and its tiny seeds are harvested to make the precious oil. So far, many clinical trials have reported beneficial effects of EPO in atopic dermatitis, though some studies differed. However, it is not well studied in the Indian population. Hence, we undertook this study to evaluate the efficacy of EPO in the treatment of AD in our population.

METHODS

Consecutive new out-patient department (OPD) patients of a referral hospital in Kolkata diagnosed as having AD using Hanifin and Rajka criteria were allocated to two groups, using a random number table. Pregnant and lactating women, epilepsy patients, those with history of peptic ulceration, intake of phenothiazines, patients who received UVB phototherapy or photo-chemotherapy in the last 1 month, and patients who received systemic steroid or other immunosuppressive drugs in the last 3 months were excluded. Informed consent was duly obtained from patients/guardians. To the first group (EPO group), evening primrose oil was supplied as 500 mg oval clear unmarked capsules containing oil, which comprised 8 to 10% of GLA, with 10 IU of vitamin E added as antioxidant. To the other (placebo) group, placebo capsules identical in appearance and containing 300 mg of sunflower oil with 10 IU of vitamin E were given. Dose of the medicine was 1 to 4 capsules/day for patients up to 1 year of age, 5 to 6 capsules/day for those aged 2 to 5 years, 7 to 8 capsules/day for those aged 6 to 10 years, 9 to 10 capsules/day for those aged 11 to 16 years, and 12 capsules/day for patients above 16 years of age-all in two divided doses were given orally. To avoid effect of varying dose on response, all the patients were given maximum acceptable dosage. Patients of both groups were advised liberal application of emollients. Treatment continued for a period of 5 months for each patient. On the first visit, apart from taking detailed history, general survey, and systemic examination, baseline assessment of the disease was made and recorded in a pre-designed clinical evaluation sheet. Four major parameters of the disease, viz., extent, intensity, dryness, and itching, were categorically recorded. Regarding extent of the disease, if only one area of predilection or less than 20% of body surface area (BSA) was involved, score was 1. If two to three areas or $<40\%$ of BSA was involved, the patient scored 2. For any involvement more than the aforementioned, the score was 3.

Regarding intensity of the disease, individual scores from 6 separate clinical items - erythema, edema/papulation, vesiculation/oozing/crusting, excoriation, scaling, and lichenification (each graded as 0, 1, 2, and 3 for absence, mild, moderate, and severe degrees) - were summated to develop 'Intensity Item Score Aggregate (IISA),' which reflects the actual intensity of the disease. From this IISA, 'intensity score' was derived. For IISA 0, intensity score was 0. For IISA 1 to 6, score was 1. For IISA 7 to 12, score was 2; while for IISA 13 to 18, intensity score was 3. Dryness was evaluated only on uninvolved areas as follows: absence - score 0; mild - score 1; moderate - score 2; and severe - score 3. Itching was also graded as 0, 1, 2, and 3 for absence, mild, moderate, and severe degrees, respectively. Total score was arrived at by adding all 4 major parameter scores. The case was labeled as mild, moderate, or severe when the total score ranged from 1 to 4, 5 to 8, and 9 to 12, respectively.

Study subjects were instructed to attend OPD at regular intervals of 4 weeks for clinical evaluation. In each subsequent visit, clinical evaluation of the change of disease status was made relative to the baseline. If total score approached $\leq 25\%$ of the baseline, we noted it as marked improvement. If total score was $>25\%$ but up to 50% of baseline, it was noted as moderate improvement. Score $>50\%$ but up to 75% of baseline was termed as mild improvement. In case of marginal improvement, score was $>75\%$ but up to 99% of

baseline. If score remained unchanged, it was called static. Score more than baseline value was termed deterioration. Last three types of changes (marginal improvement, static, and deterioration) were regarded as 'no improvement.'

On each visit, patients were observed for any adverse effect, which, if found, was recorded. Data of first 25 patients from each group who completed the 5 months of trial were compiled and analyzed using MS Excel and using unpaired *t* test.

Table 1: Breakup of study cases in relation to potential confounding factors

		EPO group	Placebo group
Age (years)	Up to 10	11 (44)	11 (44)
	11 to 20	7 (28)	3 (12)
	21 to 30	3 (12)	6 (24)
	31 to 40	3 (12)	3 (12)
	>41	1 (4)	2 (8)
	Mean	16.09	17.46
	Range	0.3 (4 months) to 46	1 to 42
Sex	Male	11 (44)	7 (28)
	Female	14 (56)	18 (72)
Baseline disease status	Mild AD	3 (12)	3 (12)
	Moderate AD	19 (76)	21 (84)
	Severe AD	3 (12)	1 (4)
Family history of atopy		15 (60)	16 (64)

EPO: Evening primrose oil, Figures in parentheses are in percentages

RESULTS

There were 65 patients at the beginning of study: 29 belonged to the EPO group, while 36 belonged to the control group [Table 1]. However, 26 patients of EPO group and 27 of the control group completed the study. Of those, the first 25 patients from each group were analyzed for the sake of simplicity. The numbers of dropouts from the EPO and control groups were 3 and 9, respectively.

Compared to the baseline values, all the mean scores in EPO group reduced gradually and progressively down on their 5 consecutive monthly assessments (M1 to M5) [Table 2]. At the end of the first month, intensity and itching were significantly reduced. Thereafter, reduction of mean values of every clinical parameter, as well as total score, assumed statistical significance. Decline was also more in intensity and itching scores. Contrarily, reduction of mean scores in the placebo group was delayed, less marked, and inconsistent. Improvement in all parameters barring intensity in the placebo group was transient too, as it did not persist till the end of the trial period (M5).

Table 3 summarizes outcome of AD in the two groups of patients based on reduction of total score of the disease.

Table 2: The scores of study cases at baseline and at five monthly evaluations

		Base-line	1 month	2 months	3 months	4 months	5 months
		Mean ± Standard deviation *P* value (unpaired t test)					
Extent	EPO	1.92±0.7	1.68±0.69	1.44±0.58 *P*<0.005	1.04±0.45 *P*<0.000001	0.88±0.44 *P*<0.00001	0.68±0.47 *P*<0.00001
	Control	1.84±0.62	1.84±0.55	1.56±0.65	1.52±0.65 *P*<0.05	1.52±0.77	1.76±0.66
Intensity	EPO	2.12±0.6	1.6±0.5 *P*<0.0001	1.08±0.4 *P*<0.00001	0.92±0.27 *P*<0.00001	0.88±0.44 *P*<0.00001	0.72±0.54 *P*<0.00001
	Control	1.48±0.5	1.44±0.5	1.28±0.45	1.32±0.55	1.2±0.5 *P*<0.025	1.24±0.43 *P*<0.05
Itching	EPO	1.76±0.59	1.12±0.52 *P*<0.00003	1±0.57 *P*<0.0003	0.56±0.5 *P*<0.00001	0.48±0.58 *P*<0.00001	0.32±0.47 *P*<0.00001
	Control	1.76±0.59	1.56±0.58	1.44±0.5 *P*<0.05	1.48±0.65	1.6±0.76	1.6±0.64
Dryness	EPO	1.2±0.57	1.2±0.57	0.88±0.66 *P*<0.05	0.88±0.66 *P*<0.05	0.56±0.58 *P*<0.001	0.52±0.5 *P*<0.00003
	Control	1.4±0.64	1.4±0.64	1.28±0.67	1.2±0.64	1.12±0.72	1.16±0.74
Total score	EPO	7±1.75	5.96±1.61 *P*<0.0228	4.4±1.55 *P*<0.00001	3.4±1.38 *P*<0.00001	2.8±1.47 *P*<0.00001	2.24±1.45 *P*<0.00001
	Control	6.48±1.44	6.24±1.5	5.66±1.5 *P*<0.0228	5.52±1.7 *P*<0.022	5.4±2.1 *P*<0.0228	5.76±1.78

EPO: Evening primrose oil

Table 3: Effect on Evening primrose oil versus placebo on total scores of patients of Atopic dermatitis

			1 month	2 months	3 months	4 months	5 months
Improved	Marked improvement	EPO	0	0	8 (n=2)	24 (n=6)	36 (n=9)
		Placebo	0	0	0	8 (n=2)	0
	Moderate improvement	EPO	0	28 (n=7)	52 (n=13)	52 (n=13)	56 (n=14)
		Placebo	0	8 (n=2)	16 (n=4)	8 (n=2)	8 (n=2)
	Mild improvement	EPO	32 (n=8)	56 (n=14)	36 (n=9)	16 (n=4)	4 (n=1)
		Placebo	20 (n=5)	28 (n=7)	20 (n=5)	24 (n=6)	24 (n=6)
Not improved	Marginal improvement	EPO	32 (n=8)	12 (n=3)	4 (n=1)	8 (n=2)	4 (n=1)
		Placebo	20 (n=5)	28 (n=7)	16 (n=4)	16 (n=4)	24 (n=6)
	Static	EPO	36 (n=9)	4 (n=1)	0	0	0
		Placebo	40 (n=10)	12 (n=3)	32 (n=8)	28 (n=7)	16 (n=4)
	Deterioration	EPO	0	0	0	0	0
		Placebo	20 (n=5)	24 (n=6)	16 (n=4)	16 (n=4)	28 (n=7)

EPO: Evening primrose oil, All figures are in percentages and figures in parenthesis indicate number of patients

Overall, at the end of the fifth month, 24 (96%) patients of the EPO group and 8 (32%) patients of the placebo group showed improvement. There was significant difference in outcome of treatment between the two groups ($P < 0.00001$, *t* test).

No significant adverse effect was reported by any patient/ guardian at any point of assessment in either group.

DISCUSSION

GLA was first isolated from the seed oil of evening primrose. This herbal plant was grown by Native Americans to treat swelling in the body. In the 17th century, it was introduced to Europe and became a popular folk remedy, earning the name *king's cure-all*. In 1919, Heiduschka and Lüft extracted the oil from evening primrose seeds and described an unusual linolenic acid, which they named GLA.[7]

Research from the 1930s to the 1950s established that a deficit of omega-6 essential fatty acids (EFAs) leads to an inflammatory skin condition in both animals and humans. Recently, it has been established that there is no deficit of linoleic acid in atopic eczema. Concentrations of linoleic acid, instead, tend to be elevated in blood, milk, and adipose tissue of patients with atopic eczema; whereas concentrations of linoleic acid metabolites are substantially reduced. This suggests reduced conversion of linoleic acid to gamma-linolenic acid (GLA). Atopic eczema may be a minor inherited abnormality of EFA metabolism.[8]

From GLA, the body forms dihomo-gamma-linolenic acid (DGLA). This is one of the body's three sources of eicosanoids (along with arachidonic acid and eicosapentanoic acid). DGLA is the precursor of the prostaglandin PGH1, which in turn forms PGE_1 and thromboxane A_1 (TXA_1). PGE_1 has a role in regulation of immune system function. TXA_1 modulates the pro-inflammatory properties of the thromboxane TXA2. Unlike other eicosanoids, DGLA cannot yield leukotrienes. However, it can inhibit the formation of pro-inflammatory leukotrienes from arachidonic acid.[9] This anti-inflammatory and immunomodulatory role of GLA has been utilized in the treatment of various diseases involving diverse systems.

The first disease for which EPO was used (for its content of GLA) was multiple sclerosis.[10] Preliminary studies suggest that GLA may have some therapeutic efficacy in diverse conditions like atopic dermatitis, rheumatoid arthritis, Sjogren's syndrome, osteoporosis, alcoholism, obesity, attention deficit and hyperkinetic disorder, pre-menopausal syndrome and diabetes. With supplementation of GLA via EPO in patients of AD, ready made GLA can directly enter the linoleate metabolic pathway, bypassing the defective rate-limiting enzyme delta-6-desaturase, and gradually restore the deficient anti-inflammatory prostaglandin (PGE1) in the body. In the present study, we found evening primrose oil (as a source of GLA) to be an effective and safe oral medication in the management of AD. Improvement in overall severity of disease started as early as the end of the 1st month of treatment with EPO; and at the end of the 5th month, 96% of the patients showed improvement. There was no drug-related adverse effect.

Many well-designed studies in the western world revealed similar beneficial effect of EPO on AD in the pediatric age group.[11-13] A large Italian study on infants and children (mean age, 11.4 months) revealed that GLA administered for 4 weeks, in addition to emollients and antihistaminics, was a safe and effective adjuvant therapy for AD.[11] A meta-analysis published in 1992 observed that controlled

trials (mostly on children) following a parallel study design showed marked improvement in atopic eczema. Patients treated with the drug showed less inflammation, dryness, scaling, and overall severity compared to controls.[12] Some other studies confirmed the beneficial role of EPO in adult atopic eczema as well. In an Italian study on 60 patients with atopic dermatitis (30 males and 30 females, 15-30 years old), 30 patients were treated with gamma-linolenic acid of (C18:3 *n*-6) at a dosage of 274 mg twice a day; the other 30 patients were given placebo. The patients were treated for 12 weeks, during which their symptoms were assessed on a linear scale, both by a dermatologist and by themselves, every 4 weeks. The patients who received gamma-linolenic acid showed gradual improvements in pruritus, erythema, vesiculation, and oozing, which were statistically significant compared with the control group ($P < 0.001$).[14] A Korean study on 14 adult patients found that after the treatment with EPO, the extent of skin lesions and pruritus was markedly reduced in all patients. While serum interferon-gamma levels were significantly increased ($P < 0.01$) after the treatment to those of the normal control group, serum IgE levels showed a significant decrease ($P < 0.05$) though failing to normalize completely. The authors concluded that EPO could be highly effective in the treatment of a grossly noninflammatory type of AD, and the restoration of serum IFN-gamma levels indicates that EPO might exert its effect through the modulation of the immunological mechanism involving IFN-gamma.[15]

A meta-analysis of a large number of studies with patients from 1 to 60 years of age in 1989 showed that effect of EPO was almost always significantly better than that of placebo. Nine controlled trials of evening primrose oil were performed in eight centers. Four of the trials were parallel; and 5, cross-over. In the analysis of the parallel studies, both patient and doctor scores showed a highly significant improvement over baseline ($P < 0.0001$) due to Epogam® (EPO): for both scores the effect of Epogam® was significantly better than that of placebo. Similar results were obtained on analysis of the cross-over trials; but in this case, the difference between Epogam® and placebo in the doctors' global score, although in favor of Epogam®, failed to reach significance. The effects on itch were particularly striking. There was no placebo response to this symptom, whereas there was a substantial and highly significant response to Epogam® ($P < 0.0001$).[16]

Some degree of improvement in extent, intensity, itching, and dryness was also noted in our patients treated with placebo. But these observations were inconsistent, non-progressive, and non-uniform. Beneficial effect of topical emollient (which was allowed in both EPO and placebo groups), inherent placebo response, and natural fluctuation in course of AD may be the likely explanation for such erratic improvement in some placebo-treated patients. However, poor response to placebo may be the cause of higher rate of defaulter (25% versus 10.34%) in the placebo group compared to the EPO group.

However, no studies could demonstrate significant effect of evening primrose oil in the treatment of AD. In a large meta-analysis, publications of clinical trials were searched in a systematic way and the study characteristics assessed independently by three assessors. Nineteen trials of gamma-linolenic acid (GLA) and 5 trials of fish oil matched inclusion criterion of placebo-controlled trial. The effect size of GLA supplementation on the improvement of overall severity of AD could be calculated from 11 of these trials. The pooled effect size was 0.15 [95% confidence limits (CL), - 0.02, 0.32]. The effect size of fish oil supplementation, calculated from 3 trials was - 0.01 (95% CL, - 0.37, 0.30).

For component subscales such as itch, scaling, and lichenification, EFA supplementation showed no benefit.[17] Another study on 102 patients at Leicester Royal Infirmary, UK, found no effect of essential fatty acid supplementation in AD.[18] Among other sources of GLA, hempseed oil was effective,[19] while borage seed oil was not.[20]

Dietary supplementation could not prevent expression of AD in infants at high familial risk, but it tended to alleviate the severity of AD in later infancy in these children.[21]

Several confounding variables such as racial factors, concomitant use of corticosteroid, etc., that are now being unearthed by recent studies may account for historically reported inconsistent patient response to EPO.[22] Recent researches have uncovered unique complexities in fatty acid metabolism and immune response in the atopic condition beyond those previously reported and may soon identify subcategories of non-responders and help establish those that can consistently derive significant benefit.

There is a paucity of trials of efficacy of EPO on AD in Indian patients. Genetic and environmental factors are known to play an important role in the development of AD. Since our randomized placebo-controlled study proved EPO to be beneficial in the management of AD, we may reasonably hope that similar studies carried out in the Indian context will also throw up encouraging results.

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