

JPPT | Single-Center Controlled Study

Evaluating the Effect of Eicosapentaenoic Acid in Children With Atopic Dermatitis: A Randomized Triple-Blind Clinical Trial

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OBJECTIVE To evaluate the effects of dietary eicosapentaenoic acid (EPA) in children with atopic dermatitis.

METHODS Forty-eight children with atopic dermatitis were randomly allocated to receive either 250 mg twice daily EPA (n = 24) or placebo (n = 24) for 4 weeks. The absolute improvement in the SCORing Atopic Dermatitis (SCORAD) index and the necessity to use topical corticosteroids was evaluated.

RESULTS Based on an intention-to-treat analysis, after 2 weeks the scores decreased to 30.50 ± 8.91 and 38.34 ± 10.52 in the EPA and placebo groups, respectively ($p = 0.015$). Per-protocol analysis showed a decrease in scores to 18.01 ± 10.63 in the EPA group and to 30.11 ± 9.58 in the placebo group ($p = 0.001$). After 2 weeks, corticosteroid was needed in 11 (50.0%) patients in the EPA group and 14 (58.3%) patients in the placebo group ($p = 0.571$), and after 4 weeks, it was needed in 7 (33.3%) patients in the EPA group and 14 (63.6%) patients in the placebo group, respectively ($p = 0.047$).

CONCLUSIONS Our results show significant favorable effects of EPA on the SCORAD scale and with regard to the necessity for corticosteroid readministration. Few adverse effects were reported in the 2 groups. We conclude that EPA supplementation is a well-tolerated and effective add-on strategy for reducing the severity of atopic dermatitis in children.

ABBREVIATIONS AA, arachidonic acid; AD, atopic dermatitis; ALA, alpha-linolenic acid; ANOVA, analysis of variance; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GI, gastrointestinal; ITT, intention to treat; LA, linoleic acid; PUFA, polyunsaturated fatty acid; SCORAD, SCORing Atopic Dermatitis; TCS, topical corticosteroids

KEYWORDS atopic; dermatitis; dietary supplement; eczema; eicosapentaenoic acid; pediatrics

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Introduction

Atopic dermatitis (AD) is a common skin disorder in children and adults. It is a chronic allergic problem¹ associated with high serum concentrations of immunoglobulin E and presents predominantly in patients with a personal or family history of eczema, asthma, and allergic rhinitis.² Environmental or food allergens contribute to more severe forms of the disease.^{3,4} In addition, genetic, dietary, and immunological factors affect progression of the disease.⁵ Evidence supports the role of dietary and lifestyle factors in triggering or subsiding the manifestations of atopy.⁶

Most dietary fat sources today are from liquid vegetable oils (e.g., soybean, sunflower, cottonseed, and corn oil) consisting of polyunsaturated fatty acids (PUFAs), especially linoleic acid, which is a type of omega-6 fatty acid (n-6) and is the precursor of arachidonic acid (AA).⁷ The highest proportion of omega-3 fatty acids (n-3) in our diets comes from alpha-linolenic acid (ALA); ALA is

the parent molecule of the n-3 family that is converted to eicosapentaenoic acid (EPA) and then docosahexaenoic acid (DHA). These 2 acids have greater biological potency than does ALA and are competitors of AA for cyclooxygenase-1 and lipoxygenase. Eicosanoids derived from AA have proinflammatory and immunoactive properties, while eicosanoids derived from EPA and DHA have an anti-inflammatory function.

High amounts of n-6 intake with low amounts of effective n-3 content in the Western diet affect the n-6/n-3 ratio and theoretically could change inflammatory responses.⁷ Some studies^{8,9} suggest the importance of n-6/n-3 dietary ratios in the inflammatory response and others¹⁰ link this ratio to the etiology of some inflammatory and autoimmune disorders. The optimal ratio of n-6 to n-3 varies in different studies. The ideal ratio appears to be 1:1 to 6:1, but the Western diet can produce ratios of >25:1; this change in balance is an important determinant in the developing nervous system, increasing the risk of coronary heart disease, hypertension, certain cancers,

diabetes, and possibly neurodegenerative diseases in addition to autoimmune disorders.¹¹ The rate of ALA conversion into EPA and the factors that may interfere with this conversion are discussed elsewhere.¹²

Studies^{13,14} have found an association between the patterns of consumption of n-6 and n-3 PUFAs and the incidence and prevalence of atopic hypersensitivity or its clinical manifestations (e.g., AD, allergic rhinitis, and asthma). In addition, some investigators^{15,16} have reported a causal relationship between fatty acid consumption and severity of allergic manifestations. Furthermore, it has been reported¹⁷ that EPA inhibits interleukin (IL)-6, IL-8, and tumor necrosis factor- α through free fatty acid-binding proteins. n-3 supplementation may reduce the intensity of itching and severity of the skin lesions in AD,¹⁸ and EPA supplementation could prevent recurrence of skin lesions in cases of occupational dermatitis.¹⁹

Animal studies²⁰ have shown that treatment with DHA/EPA decreases the clinical score of dermatitis and lowers local leukotriene B4 concentrations. Also, higher maternal and infant ratio of n-3 was associated with lower prevalence of immunoglobulin E-mediated allergic diseases.²¹ However, clinical studies are still needed to evaluate if EPA supplementation other than ALA positively affects AD patients. Fish oil is the primary source of EPA and DHA. The quality of fish oil supplements to balance the n-6/n-3 ratio is best expressed in terms of its EPA and DHA content; however, because EPA may play a more important role in regulating inflammatory mechanisms than does DHA, the amount of EPA could also be more important. This randomized, blinded clinical trial was aimed at evaluating the effect of dietary supplementation with pure EPA in children with AD.

Materials and Methods

Patients and Setting. This is a prospective, blinded, randomized controlled trial, approved by the deputy of research of Shahid Beheshti University of Medical Sciences and the research committee of Mofid Children's Hospital, which is affiliated with the College of Medicine. The participants were pediatric patients with AD who were referred to the pediatric dermatology or allergy, asthma, and immunology clinic of Mofid Children's Hospital in Tehran from May 2018 through April 2019.

Inclusion and Exclusion Criteria. We included children aged 3 months to 18 years with a diagnosis of AD based on the Rajka-Hanfin criterion. The diagnosis of AD requires meeting 3 major and 3 minor criteria.¹ The diagnosis was made by an experienced pediatric dermatologist or allergy specialist. Patients were excluded from the study if they had irregular medication usage (defined as 3 missed medication doses within 4 weeks), if their clinical condition was deteriorating, if they had skin problems other than AD or severe systemic diseases, if their skin involvement involved <2% or >30% of their body surface area, if they had any history of hypersensitivity to any components of the prescribed

product, or if they had any history of systemic corticosteroid use 4 weeks before or any topical corticosteroid (TCS) use 2 weeks before study enrollment.

Randomization and Patient Enrollment. An online software program (<https://www.sealedenvelope.com/>) was used to generate randomized blocks for assigning patients to 2 groups of equal size. To the best of our knowledge, there has been no previous study reported in the literature regarding EPA administration in children with AD. However, in 1988, Bjørneboe et al¹⁸ published a study in which they investigated the effect of fish oil supplementation in patients with AD. Its results were used to calculate the effect size and to estimate the sample size needed. Their results showed that the itching score reported by patients at the end of 3 months in the intervention group was 2.6 ± 2.7 , and in the placebo group the score was 5.2 ± 2.7 . The effect size based on these results was equal to 1.03; considering this large effect size, the research team decided to carry out our calculations based on a standard effect size equal to 0.8 to calculate the sample size to detect any discrepancy between 2 independent means. Considering this effect size with a 2-tailed p value of <0.05 as statistically significant (see Statistical Analysis section), 21 participants in each group were required. We added 4 additional patients in the anticipation of a 10% loss to follow-up. Thus, a total of 48 patients with AD were allocated to 2 groups of 24 patients each.

Patients in the EPA group received oral EPA softgels (250 mg twice daily) for 4 weeks (Epastigel, Pars Pharmed Pharmaceutical Co, Ltd, Tehran, Iran). The placebo group received a placebo with the same shape, taste, and color, which was administered using the same schedule as for the EPA. The placebo softgels were produced in accordance with good manufacturing practices in a pharmaceutical plant and were filled with food-grade paraffin. To administer the EPA or placebo, for those patients who could not swallow the softgels, caregivers learned to draw the oily contents from the softgels with a 0.5-mL syringe and drained half of it at one meal and the other half at another meal comprising food or milk.

Both groups received conventional AD treatments, which consisted of topical emollients (e.g., Eucerin) and TCS. For the TCS, we used hydrocortisone acetate 1% ointment, administered twice daily to the affected area. Demographic parameters and medication and medical history of participants were recorded at baseline. The diet regimen was the same for both groups relative to seafood consumption, the primary and most abundant source of dietary EPA and DHA. Patients' families were instructed to serve seafood for 1 to 3 meals per week.

Outcome Measures. The SCORing Atopic Dermatitis (SCORAD) is a 3-criteria questionnaire that calculates the patient's score based on involved area, intensity of eczema, and subjective symptoms (itching and sleeplessness). The total score ranges from zero to 103.

Table 1. Baseline Characteristics of the 2 Study Groups

Variable	Study Groups		p value
	EPA (n = 23)	Placebo (n = 23)	
Age, mean ± SD, mo	30.96 ± 23.10	39.65 ± 29.34	0.242
Sex, n (%)			
Male	12 (52.2)	13 (56.5)	0.500
Female	11 (47.8)	10 (43.5)	
History of AD			
New patient, n (%)	15 (65.2)	18 (72.0)	0.613
Duration of AD in all patients, mean ± SD, mo	2.69 ± 4.75	2.89 ± 4.23	0.875
Drug history, n (%)			
Antihistamine use	11 (47.8)	15 (65.2)	0.398
Topical glucocorticoid use	23 (100.0)	23 (100.0)	1.000
Topical Eucerin use	17 (73.9)	20 (80.0)	0.616
Past medical history, n (%)			
History of GERD	10 (43.5)	10 (43.5)	1.000
Other irrelevant diseases*	5 (21.7)	4 (17.4)	0.817
Allergy history, n (%)			
Food and drug allergy	10 (43.5)	8 (34.8)	0.412
Family history of allergies	9 (39.1)	8 (34.8)	0.606
SCORAD, mean ± SD	49.65 ± 8.29	46.91 ± 11.37	0.504

AD, atopic dermatitis; EPA, eicosapentaenoic acid; GERD, gastroesophageal reflux disease; SCORAD, SCORing Atopic Dermatitis index

* Included 2 children with attention deficit hyperactivity disorder, 1 autism spectrum, 1 nephrotic syndrome, 2 epilepsies, 1 thalassemia minor, 1 congenital heart disease, and 1 patient with history of orthopedic surgery for congenital syndactyly in 2 toes.

In this study the online calculator (<http://scorad.corti.li/>) was used at baseline and follow-up visits in the second and fourth weeks of the study.²² One trained physician was assigned to do the scoring.

Statistical Analysis. The frequency of patients who needed TCS was reported as an indicator of disease severity. The intention-to-treat (ITT) patients were identified after randomization and before treatment completion at 4 weeks. For statistical analysis, the Shapiro-Wilk test was used to determine the normality of quantitative variables. An independent Student's *t*-test was used to compare the mean values between the groups, and the changes in SCORAD score from baseline to 4 weeks were analyzed using mixed analysis of variance (ANOVA). For mixed ANOVA, the sphericity of the SCORAD data was assessed with the Mauchly test, and if the assumption of sphericity was violated, the Greenhouse-Geisser correction was used for correcting the degrees of freedom; a *p* value of <0.05 was considered as the level of statistical significance. For evaluating the frequency of patients who needed readministration of topical corticosteroids, the χ^2 test was used. The data were analyzed with IBM SPSS Statistics for Windows (version 22.0; IBM, Armonk, NY).

Results

In this study, 48 patients were enrolled, and 43

patients finished the last follow-up per protocol. Two patients (one in each group) did not continue the study because of diarrhea and gastrointestinal (GI) upset before the second visit, and 3 patients (2 patients in the placebo group and 1 patient in the EPA group) were lost in a 4-week follow-up. The 2-week follow-up results of the last patients were used in ITT analysis. The diagram of the Consolidated Standards of Reporting Trials of the current study is shown in the Supplemental Figure.

The mean age of patients in the EPA group was 30.96 ± 23.10 months, and mean age was 43.52 ± 39.87 months in the placebo group (*p* = 0.184). The sex ratio (men:women) in the EPA group and placebo group was 12:11 and 13:12, respectively (*p* = 0.990). The demographic features shown in Table 1 were not significantly different between the 2 groups.

At the beginning of our study, the SCORAD score was 49.65 ± 8.29 in the EPA group and 46.91 ± 11.37 in the placebo group (*p* = 0.504). Intention-to-treat analysis showed that after 2 weeks the SCORAD score was decreased to 30.50 ± 8.92 in the EPA group and 38.34 ± 10.52 in placebo group, with the difference being statistically significant (*p* = 0.005), and per-protocol analysis revealed that the SCORAD score significantly decreased to 10.63 ± 9.58 in the EPA group and 18.01 ± 30.11 in the placebo group (*p* = 0.001). The mean percentage of decrease in SCORAD was higher in the EPA group (18.14 ± 2.62 vs 9.03 ± 4.01; *p* < 0.001). The within-

Table 2. Within- and Between-Group Comparisons of SCORAD Scores*

	EPA†	Placebo	p value‡
Baseline	49.65 ± 8.29	46.91 ± 11.37	0.504
After 2 wk	30.50 ± 8.92	38.34 ± 10.52	0.005
After 4 wk	10.63 ± 9.58	18.01 ± 30.11	0.001
p value‡	<0.001	<0.001	

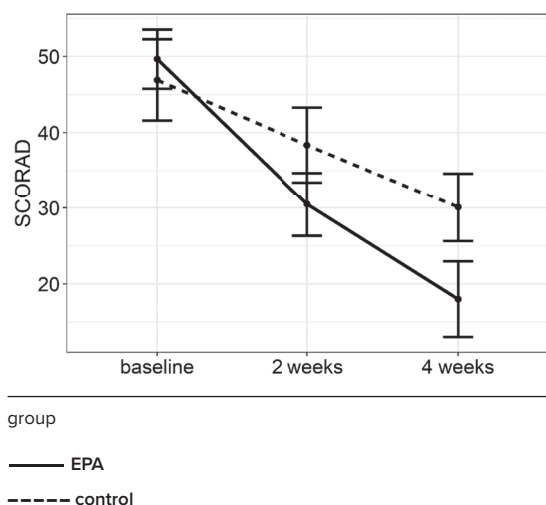
EPA, eicosapentaenoic acid; SCORAD, SCORing Atopic Dermatitis index

* Data presented as mean ± SD.

† p values between each treatment group analysis.

‡ p values for changes over time within each treatment group.

Figure 1. Trend in changes between the SCORing Atopic Dermatitis (SCORAD) index for eicosapentaenoic acid (EPA) and placebo groups using intention-to-treat results.



group analysis demonstrated that both groups had a significant decrease in their scores compared with the starting point ($p < 0.001$), although the between-group analysis did not present this difference ($p = 0.07$). These results are summarized in Table 2 and Figure 1.

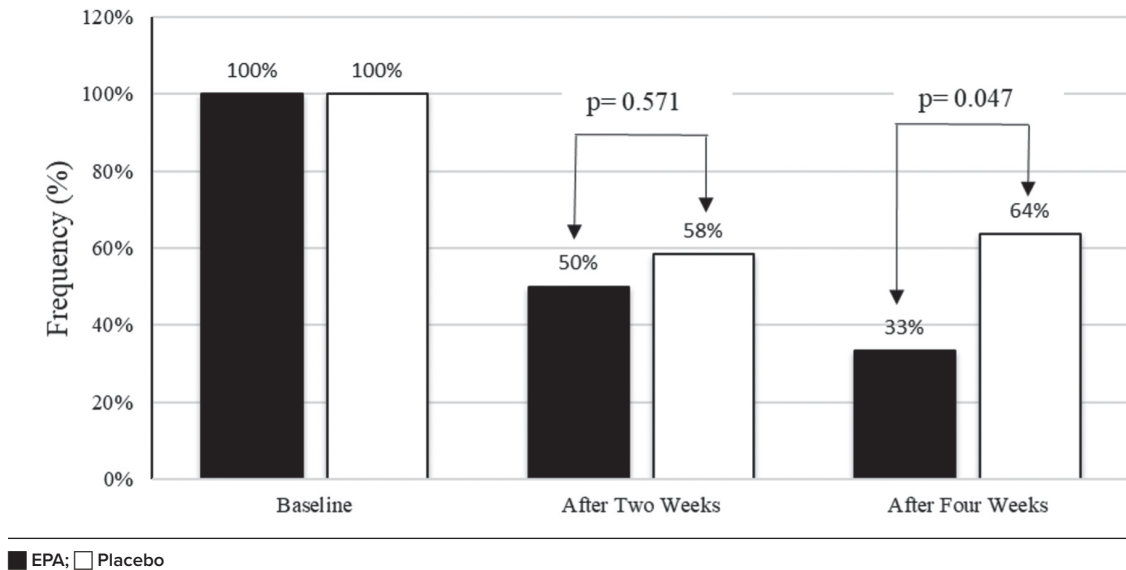
We carried out mixed ANOVA to compare the 2 groups in terms of the pattern of change in SCORAD. The Mauchly test showed that the assumption of sphericity was violated for the score data: $W = 0.611$; $p < 0.001$. Therefore, the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity, $\epsilon = 0.72$. The main group effects approached significance [$F(0.7, 23.2) = 3.487$; $p = 0.069$; $\eta^2 = 0.08$], and the main effect of time was significant [$F(1.2, 46.4) = 836.958$; $p < 0.001$; $\eta^2 = 0.51$]. In addition, the interaction effect of group \times time was significant: $F(1.2, 46.4) = 82.704$; $p < 0.001$; $\eta^2 = 0.09$. Therefore, EPA showed a different pattern of decrease in SCORAD compared with the control.

The necessity of continuation of TCS in the second and third follow-up clinic visits was also assessed. Although TCS was needed in all patients at the pre-therapy baseline evaluation, TCS was administered in 11 (45.8%) patients in the EPA group and 14 (58.3%) patients in the placebo group ($p = 0.571$) at 2 weeks, and 7 (33.3%) patients in the EPA group and 14 (63.6%) patients in the placebo group needed TCS ($p = 0.047$) at 4 weeks. Three patients in the placebo group needed readministration of TCS, although their TCS was discontinued during the last visit (Figure 2). At the baseline, the mean SCORAD for the total sample was 48.26 ± 9.21 . At 2 weeks after the intervention, the mean scores were 40.76 ± 7.04 and 26.73 ± 6.43 ; and at 4 weeks after the intervention they were 30.69 ± 10.54 and 16.73 ± 10.54 in patients with and without continuation of TCS, respectively (all $p < 0.001$).

Overall, a few adverse effects of treatment were reported by our patients. Diarrhea, GI upset, and nausea were reported by 1, 1, and 2 participants in the EPA group, respectively, and by 2, 1, and 1 participants in the control group, respectively. If the adverse effect was tolerable for the patient, the patient was advised to tolerate it; otherwise the patient was excluded from the study. If at least 2 weeks had passed since the start of the treatment, the patient's results were included in the ITT analysis. As noted above, 2 patients (one in each group) did not continue the study because of diarrhea and GI upset before the second visit. Overall, we believe the 2 groups were similar in manifestation of GI complaints.

Discussion

According to the results of this study, the severity of eczema in patients with AD in the EPA group was significantly lower than for those in the placebo group at both the end of the 2-week ($p < 0.05$) and the 4-week ($p < 0.001$) study periods. The SCORAD score in both groups decreased significantly (see Table 2). The significant differences in the main effects of group and time and in the interaction effect of group \times time indicated that the groups differed in SCORAD at each time point, and, therefore, the pattern of change is also different

Figure 2. Topical corticosteroid usage.

between the 2 groups. The secondary outcome of our study involved the readministration of TCS. The necessity of continuing TCS significantly differed at the end of the study ($p < 0.05$). There were no differences in side effects between the 2 groups. Therefore, supplementation with EPA could be considered a safe and effective intervention by which to reduce the severity of eczema in patients with AD.

Recent studies indicate that PUFAs, as components of cellular membranes and precursors of immunomodulators, play a significant role in the pathogenesis of AD. In addition, dietary fats with a high content of PUFAs play a role in the pathogenesis of AD.²³ Generally, cooking oils (sunflower, soybean, and canola oils) with an herbal origin have a high content of PUFAs, especially linoleic acid (LA), but a lower content of n-3 PUFAs.²⁴ Progressive increase in LA dietary intake combined with a reduction in consumption of n-3 long-chain PUFAs such as EPA and DHA leads to an imbalance in eicosanoid pro-inflammatory cytokines.²⁵ An explanation for this result is that LA is converted to AA, which is the precursor of inflammatory prostaglandins, leukotrienes, and prostacyclins, while ALA is converted to EPA and subsequently to DHA. These metabolites (i.e., AA, EPA, and DHA) are known to be the most biologically potent precursors of noninflammatory mediators. The rate of ALA conversion into EPA could be diminished by high intake of LA; deficiency of some nutrients such as vitamin B3, vitamin B6, vitamin C, zinc, and magnesium; trans-fatty acids consumption; alcohol abuse; and hyperinsulinemia.²⁶ Also, it has recently been evidenced that the rate of conversion diminishes with some pathological conditions. Reduced conversion of ALA into EPA is partly coupled with a low level of n-3 long-chain PUFAs. Geographic areas with drought (because milk and meat of non-grass-fed

animals have a low content of n-3 PUFAs) and declining oily fish consumption can worsen the abovementioned processes.^{27–29} In support of this hypothesis, it has been reported that taking a small amount of n-3 long-chain PUFAs in daily diets is associated with changes in complex lipids and immune-related eicosanoids and increases levels of oxidized lipids and amino acids, resulting in oxidative stress and lipid peroxidation. This phenomenon may explain the increased prevalence of allergic and autoimmune disorders resulting from the industrial diets.

Previous studies³⁰ have shown that administering fish oil can improve AD symptoms. To our knowledge, no study has been designed to investigate the effect of EPA on the severity of eczema in pediatrics with AD. However, Bjørneboe and colleagues¹⁸ showed administration of fish oil at a daily dose of 10 g (containing about 1.8 g EPA) over 12 weeks was effective in 31 adult patients with AD. Also, the study investigators reported a significant reduction in the degree of itching and other related symptoms. Based on their results, the probable mechanism for this effect of EPA on the improvement of AD could be due to changes in the systemic concentrations of leukotrienes and prostaglandins. Mayser et al³¹ have reported a marked improvement from baseline with 200-mL daily infusions of an n-3 fatty acid-based lipid emulsion consisting of 10% fish oil, compared with a conventional n-6 lipid emulsion consisting of 10% soybean oil, in 22 adult patients hospitalized for moderate to severe AD. In an animal study, Yoshida et al²⁰ showed that treatment of AD with orally administered DHA/EPA in NC/Nga mice decreases the dermatitis clinical score and lowers local leukotriene B4 production in the skin. The inhibition of disease progression induced by DHA/EPA was reversed by local injection of leukotriene B4, suggesting that the therapeutic effects of DHA/EPA are

dependent on lowering systemic leukotriene B4 concentrations. Treatment of AD with DHA/EPA appears to be effective in reducing allergic skin inflammations, acting by suppressing leukotriene B4 production. Although the therapeutic effects observed in our study were statistically significant, it is reasonable to investigate the effect of EPA administration in larger populations.

This study has some limitations, including our small sample size; we did not measure EPA blood concentrations or blood concentrations of other important lipid or inflammatory mediators in our patients before starting the treatment and throughout the study, particularly if patients were EPA deficient. Although patients' families were instructed to serve seafood for 1 to 3 meals per week, their actual intake was not tracked or recorded.

Conclusion

Based on the results of our study, EPA supplementation could be considered as a safe and effective complementary strategy for reducing the severity of eczema in children with AD. This improvement is noticeable 2 weeks after starting EPA. Eicosapentaenoic acid supplementation is a safe complementary therapy, at least for a period of 4 weeks.

Article Information

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation. This study obtained approval from the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.PHARMACY.REC.1397.060), and the study protocol was approved by the Iranian Registry of Clinical Trials (www.irct.ir) (IRCT20170608034390N2). Legal guardians of patients signed an informed consent form before enrollment.

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