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Cold microfiltered seawater against atopic dermatitis in the paediatric population: pilot study

Cold microfiltered seawater and atopic dermatitis

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SUMMARY

Objective: To evaluate the efficacy of a 2.1% saline solution spray of seawater in a paediatric population with AD. Product safety and its effect on quality of life were also evaluated.

Design: A prospective, longitudinal, non-controlled, 28-day study to evaluate the clinical response of a 2.1% saline solution spray of seawater, applied twice/day.

Place: Performed in Madrid within the paediatrics setting.

Participants: Patients with AD in mild/moderate flareup phase (mean age 5.9 years). Of the 24 who met the inclusion criteria, 19 ended the study.

Method: The SCORAD SCORAD (S*COring Atopic Dermatitis),* index, the trans-epidermic water loss (TEWL) and the improvement of hydration (Corneometer®) were measured at baseline and at 2 and 4 weeks of treatment. Quality of life was measured using the IDQoL index.

Results: 83% and 94% of the patients had a significant improvement in the SCORAD index at 14 and 28 days, respectively. A significant improvement was seen in the corneometric index and the TEWL index in 76% and 75% of the patients at 14 days and in 71% and 79% at 28, respectively. The IDQoL index improved significantly in 89% of the patients.

Conclusiones: The SCORAD, corneometric and TEWL indices improved significantly in paediatric patients with AD flare-ups after application of a 2.1% saline solution spray of seawater for 28 days.

KEYWORDS: sea therapy, seawater, atopic dermatitis, flare-ups, paediatrics.

ABSTRACT

Objective: Evaluate the efficacy of a 2.1% saline spray from seawater against AD in a pediatric population. As a secondary objective, the tolerance and safety of the product were evaluated, in addition to its effect on quality of life.

Design: Prospective, uncontrolled, 28-day study to evaluate the clinical response and tolerance of a 2.1% seawater-based saline spray, applied at least 2 times / day in pediatric patients.

Setting: Pediatry in Madrid, Spain.

Participants: Patients with AD with mild or moderate flares completed the study (mean age 5.9 years). Of 24 who met the inclusion criteria, 19 finalized the study. Methods: The SCORAD atopic dermatitis index (SCORing Atopic Dermatitis), the trans-epidermal water loss (TEWL) and the improvement of hydration (Corneometer®) were measured at baseline and at 2 and 4 weeks of treatment. Quality of life was determined using the IDQoL index.

Results: 83% of them showed a significant improvement in the SCORAD index at 14 days, and 94% at 28 days. A significant improvement in the corneometric index and TEWL was observed in 76% and 75% of patients at 14 days and 71% and 79% at 28, respectively. IDQoL improved significantly at the end of the study.

Conclusions: In this study, a significant improvement in the SCORAD, corneometric and TEWL values was observed in pediatric patients with mild or moderate flare-ups of DA after applying a 2.1% seawater-based saline spray during 28 days, 2 times a day. Quality of life improved significantly at the end of treatment.

KEYWORDS: marine therapy, seawater, atopic dermatitis, flares, pediatrics.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory disease associated with skin hyperreactivity, in which flare-ups or relapses are common[1,2]. It affects about 10-20% of children[1,3]. Patients with AD suffer severe itching followed by a scratching behaviour that induces the production of pro-inflammatory cytokines. This triggers a cycle that is associated with erythema, keratosis and shedding.[1,2].

Corticosteroids and antihistamines have shown their benefit in the treatment of AD, though their side effects limit their use in the long term[1,2]. Therefore, natural products have been investigated that can be used as adjuvant therapy. It is the case of water therapy or use of water for therapeutic purposes, that has shown a beneficial effect on AD thanks to the modulation of lymphocyte proliferation and cytokine synthesis, as well as a possible antioxidant effect.[4-10]. Several authors have demonstrated the protective effect of water therapy against AD induced in murine models.[10,11]. Lee established that water taken from the deep sea prevents and treats atopic lesions by suppressing the expression of chemokines and proinflammatory cytokines and inhibiting the production of histamine and IgE, underlying in the signalling pathways STAT1 and JNK1/2.[12]. In addition, the increased epidermal thickness and mast cell infiltration were reversed after the application.([12].

The primary aim of this study was to evaluate the clinical effects of a 2.1% saline solution spray of seawater against AD in flare-ups in a paediatric population. The secondary aim was to evaluate the tolerability and safety of the product, its effect on quality of life and the degree of satisfaction of the patients with the treatment.

MATERIAL AND METHODS

A prospective, longitudinal, uncontrolled 28-day study to evaluate the clinical response and tolerability of a 2.1% saline solution spray (Quinton Medical Skin Health®, Laboratoires Quinton Internacional S.L., Alicante) for topical application in adults and children from 3 years.(14) The study was performed between May 2018 and March 2019.

The isotonic solution used is a spray containing cold microfiltered seawater according to René Quinton protocol with 2.1% salinity.[13]. It is indicated as coadjuvant symptomatic treatment for mild-moderate AD. Its posology consists of application on the area of the flare-up at least

twice a day for 4 weeks.[13].

It is a polyelectrolyte solution (Na^+, Cl^-, Mg^{2+}, K^+, Ca^{2+}, Cu^{2+}, Zn^{2+}, etc.) with organic nutrients as vitamins (D-biotin, thiamine, riboflavin, nicotinamide, cyanocobalamin, pyridoxine) and other biomolecules. Seawater is taken from plankton proliferation areas at 30 metres in depth in areas of the Bay of Biscay. This is transported refrigerated to the laboratory where, after a physico-chemical and microbiological analysis, it follows a double cold microfiltration process in compliance with the European Pharmacopoeia regulations. Then it is taken to isotony in order to obtain a salinity similar to that of a natural tear. Immediately after it, the finished product is re-analysed and packaged under aseptic conditions.

The product was applied twice a day (morning and night) for 28 days. The efficacy and tolerability endpoints of the product were evaluated at the baseline visit (T0) and at two follow-up visits, at 2 and 4 weeks of treatment (T14 and T28, respectively).

INCLUSION AND EXCLUSION CRITERIA

The study subjects should meet the following criteria: age 3-14 years, presence of atopic skin in mild (< 15) or moderate flare-up phase (from 15 to 40) according to the SCORAD index, good health condition and availability to complete the visits.

A reason for exclusion was the presence of at least one of the following criteria: inability to comply with the study protocol, presence of atopic skin in severe phase (SCORAD index > 40); diseases requiring treatments that could interfere with the product analysed; lesions with signs of infection; systemic or topical treatment with steroids or immunomodulators; simultaneous participation in another clinical trial; or surgery scheduled during the observation period.

EFFICACY AND TOLERABILITY ASSESSMENT

The SCORAD *(SCORing Atopic Dermatitis),* index, the skin barrier recovery by trans-epidermic water loss (TEWL, *Trans-Epidermic Water Loss,* con la sonda Tewameter TM300® en g/h/m²) and the improvement of hydration (by Corneometer®) after the treatment.

The SCORAD index was created and validated in 1990 by the European *Task Force of Atopic Dermatitis*[14]. It is a clinical index to know the degree, severity and seriousness of atopic rash. Six clinical signs: reddening, swelling, exudation, formation of scabs, lichenification and dryness. Its severity is established with a value scale of 1-3 (mild to severe) and noting the body areas with rash, calculating the total affected area. Symptoms related to quality of life, such as itching and sleep disturbances, are also considered. According to the final score obtained, AD is classified as mild (<15 points), moderate (14-40 points) or severe (>40 points).

The TEWL and the corneometer are the two methods most commonly used to establish the skin hydration degree. TEWL is defined as the water amount that enters from the body inside to the atmosphere by diffusion or evaporation. Its values are higher in case of dehydrated skin. The corneometer establishes the skin capacitance, that is, its capacity to maintain the electric charge. This capacitance is greater the higher the hydration.

During the treatment adverse events were recorded and monitored until they subsided.

QUALITY OF LIFE AND SATISFACTION

The infants' dermatitis quality of life (IDQoL), that measures the impact of skin diseases in the quality of life of the patients, was performed[15]. It evaluates the impact of the disease on the symptoms and sensations of the patient, daily activities, personal relations and treatment. The IDQoL is calculated adding the scores of each question, with at least 0 and a maximum of 30. The impact on the life of the patient is measured as 0-1: no effect, 2-5: slight effect, 6-10: moderate effect, 11-20: significant effect, 20-30: extremely severe effect.[16].

At the final visit, the degree of satisfaction of the patient with the treatment was evaluated with a survey to the parents or guardian. The following were rated, according to the categories "I dislike it a lot, I dislike it moderately, I dislike it a little, I like it a little, I like it moderately or I like it a lot": general opinion, appearance, odour, colour, texture, feeling in the nose, easy to apply, removal of dryness in the treated area, result on the skin, tolerance and willingness to use the study product in the future.

ETHICS

The parents or legal guardian of the minor signed the informed consent before starting the study. This was performed according to the conditions established for performing trials in humans of ICH 2016. The good clinical practice guidelines (ICH E6 BPC) were followed and conformity with the General Data Protection Regulation (GDPR) approved by Royal Decree 5/2018 was ensured. The study was authorised by the Spanish Agency for Medicinal Products and Medical Devices and approved by the Regional medicinal product Research Ethics Committee of the Region of Madrid on 19/01/2018 (DOCC-000-25-0).

STATISTICAL ANALYSIS

A descriptive analysis was performed of the quantitative biometric variables at different experimental times, including basic descriptive parameters (central trend and variation). Linear mixed-effects models were used, that were adjusted to data distributions in each variable (SCORAD scale, corneometric index, TEWL value, and IDQoL index) for the purpose of evaluating the clinical response to the treatment over the experimental times. The treatment effect on the primary variables was interpreted with reference to baseline. The models used in the study were analysed by the nlme software R package. The multiple biometric measures performed over time were considered and, therefore, correlated, when including randomised effects in each individual, allowing that the intercept of the models changed randomly among the trial individuals. A significant value of 0.05 was established (95% confidence interval).

Variable	T0	T14	T28
SCORAD scale			
Average ± standard deviation	25.88 ± 9.48	16.72 ± 10.75	12.28 ± 10.83
Median (interquartile range)	26.65 (16.0)	14.75 (16.13)	11.35 (14.20)
Range	(11.7 - 40.1)	(3.8 - 39.7)	(0 - 36.8)
Corneometric index			
Average ± standard deviation	14.63 ± 10.19	23.52 ± 8.97	26.31 ± 11.29
Median (interquartile range)	11.45 (16.43)	23.0 (12.95)	25.20 (16.05)
Range	(1.7 - 39.9)	(3.9 - 42.5)	(6.6 - 53.3)
TEWL value			
Average ± standard deviation	19.16 ± 8.43	14.58 ± 6.27	13.23 ± 4.74
Median (interquartile range)	18.36 (9.0)	12.60 (5.75)	13.65 (7.45)
Range	(7.4 - 35.3)	(7.9 - 30.4)	(6.2 - 22.6)

Table 1. Descriptive statistics of atopic dermatitis SCORAD (SCORing Atopic Dermatitis) index, corneometric index and TEWL index at each experimental time (n=19). T0: baseline; T14: day 14 visit; T28: day 28 visit.

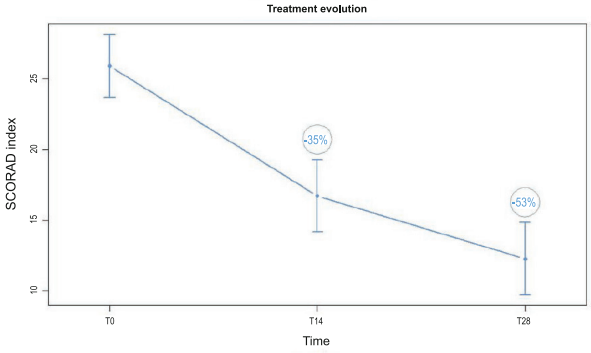

Figure 1. Evolution of SCORAD index at the study visits (mean ± standard error) according to the analysis of linear mixed-effects models (n=19). The values show the percentage reduction from the baseline value (indicating improvement). T0: baseline; T14: day 14 visit; T28: day 28 visit.

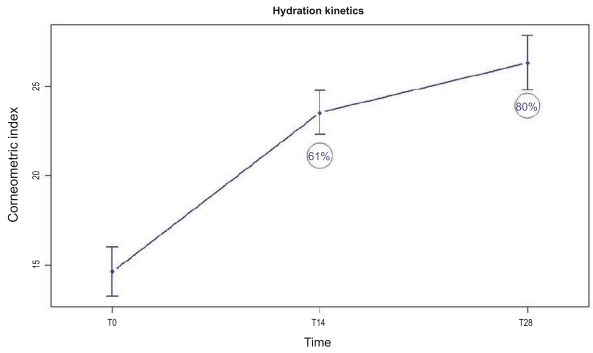

Figure 2. Evolution of the corneometric index at the study visits (mean ± standard error) according to the analysis of linear mixed-effects models (n=19). The values show the percentage increase from the baseline value (indicating improvement). T0: baseline; T14: day 14 visit; T28: day 28 visit.

RESULTS

STUDY POPULATION

Of the 24 subjects meeting the inclusion criteria, 19 ended the study. Three were excluded because their AD progressed to severe and required application of corticoids. Two patients decided to discontinue the study after the second visit due to pruritus when applying the product. Nine patients were women and 15 men, with a mean age of 5.9 years (range 3-12 years). The areas most commonly affected by AD were the arm (n=6), cheek (n=6) and leg (n=4).

SCORAD, CORNEOMETRIC AND TEWL INDICES

83% of the patients had an improvement in the SCORAD index at 14 days and 94% at 28 days (Table 1). Figure 1 represents the average trend of the data at each experimental time. All changes were statistically significant.

A significant improvement of the corneometric index was seen in 76% of the patients at 14 days and in 71% at 28 (Table 1 and Figure 2).

The percentage of patients with significant improvement in the TEWL index was 75% at 14 days and 79% at 28 (Table 1 and Figure 3).

QUALITY OF LIFE AND SATISFACTION

The IDQoL values improved significantly in 89% of the patients both at 14 (5.39 ± 3.29) and at 28 days (4.33 ± 4.59) from the baseline value (9.06 ± 5.24) (Figure 4).

In the satisfaction survey, the general opinion on the product was very good for 53% of the participants, moderately good for 42% and discreetly good for 5%. The result in the treated area was rated as very satisfactory by 37% of the participants, moderately satisfactory by 53% and somewhat satisfactory by 11%.

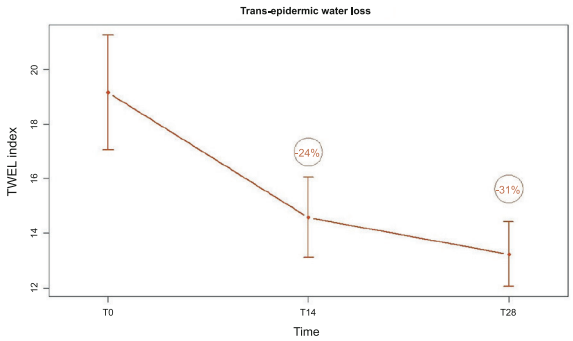

Figure 3. Evolution of the TEWL value at the study visits (mean ± standard error). The values show the percentage reduction from the baseline value. Values >40, identified as outliers, were ruled out, since they affect normality and for the purpose of finding a valid model for the data. Therefore, at T0 and T28 the n was 17 and at T14 it was 19. T0: baseline; T14: day 14 visit; T28: day 28 visit.

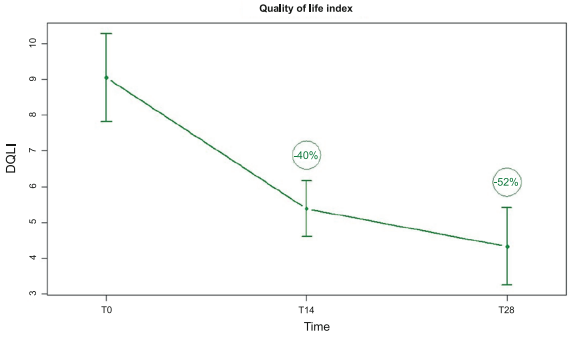

Figure 4. Evolution of the IDQoL value at the study visits (mean ± standard error) from the baseline value. The lowest scores correspond to a quality of life improvement. T0: baseline; T14: day 14 visit; T28: day 28 visit.

TOLERANCE

After 28 days of use, 16% of the participants (n=3) reported some discomfort such as itching for a few seconds upon applying the investigational product, mainly in areas with wounds due to the flare-up.

DISCUSSION

In this study a significant improvement was seen in the SCORAD, corneometric and TEWL indices in paediatric patients wit mild/moderate flare-ups of AD after the twice-a-day application for 28 days of a 2.1% saline solution spray of seawater. These benefits were evident at 2 weeks of treatment.

The pathogenesis of AD involves barrier dysfunction elements, cell-mediated immune response disorders, IgE-mediated hypersensitivity and environmental factors. In severe AD mutations have been involved that cause a loss of filaggrin function due to a possible increase in trans-epidermic water loss, pH disorders and dehydration.[16]. The lesions are characterised by infiltration of inflammatory cells. [17]. The cytokine Th2/Th1 imbalance seen in AD can modify cell-mediated immune response and promote IgE-mediated hypersensitivity.[11,18]

AD affects in particular the paediatric population, involving about 20% of the European children.(19) In this study, performed in a population aged between 3 and 12 years, the patients had a significant degree of dehydration, as shown by the average baseline values of the SCORAD index (25.9), the corneometric index (14.6) and the TEWL index (19,2).

Seawater is a polyelectrolyte solution with a complex chemical composition that contains a high diversity of majority, minority elements and trace elements. It is rich in nutrients and minerals such a Ca^{2+}, Mg^{2+}, Na^{+}, Zn^{2+}, K^{+}, Fe^{2+}, HCO3, Cl^{-} or SO4, and its intake restores mineral balance.[11,20]. It has been recognised as a natural source of minerals with potential properties against diabetes, cholesterolaemia, or obesity.[21-24]. In addition, several studies have shown the beneficial effects of water therapy on skin disorders[25-28] by modulating lymphocyte proliferation and cytokine synthesis, as well for its possible antioxidant effects[6-13].

Different therapeutic effects of seawater have been recognised[29-33], such as the EGF level increase thanks to its alkaline pH and a higher level of bicarbonate (which by reducing acidification promote restoring the mucosa); an anti-inflammatory effect due to its high potassium and magnesium concentration, that can reduce the levels of TNF, IL-8 IL-1 beta and IL-6[29,30]; and the mechanical sweeping, that removes wastes from the cell surface.

A recent study by Lee et al. has investigated the effects of water taken from the sea on atopic skin inflammation in mouse and cell lines of human keratinocytes[12]. A DA induction model was used in Nc/Nga mice treated with 2,4-dinitrochlorobenzene (DNCB). Seawater reduced different inflammatory chemokines, such as the macrophage-derived cytokine (, MDC), or the thymus- and activation-regulated chemokine (, TARC); normal T cell expressed and secreted (RANTES), as well as expression of mRNA of IL-6 and Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF).[12] These effects were mediated by the suppression of phosphorylation of STAT1 (signal transducer and activator of transcription). A reduction was shown in the serum levels

of IgE, IL-4 and histamine. In addition, after the application of seawater the increased epidermal thickness and mast cell infiltration caused by DNCB were reversed.[12] This re-establishment of skin health was attributed to the positive regulation of filaggrin, the recovery of involucrin expression and the inhibition of IL-4 production.[12]

Other trials have shown protective effects of water therapy against DNCB-induced AD. Bak et al. applied for 6 weeks concentrated seawater to atopic skin lesions induced by DNCB in Nc/Nga mice.[10] The treatment reduced the severity of symptoms, including oedema, erythema, dryness, itching and trans-epidermic water loss. Epidermal thickness and inflammatory cell infiltration were reduced after treatment. Positive regulation of IgE, histamine and proinflammatory cytokines in serum was inhibited, and the CD4+/CD8+ ratio was reduced in splenic lymphocytes. Furthermore, cytokine levels decreased, in particular IL-4 and IL-10, which are important for the development of Th2 cells.[10]

All parameters tested in our study evidenced a significant improvement that was detectable at 14 days of spray application. The SCORAD value, indicating the severity of AD, was reduced from baseline by 35% and 53% at 2 and 4 weeks, respectively. Virtually all the population had this index improved at the end of treatment. The parameters evaluating skin hydration levels also improved remarkably. The corneometric index improved by 61% and 80% at 2 and 4 weeks, respectively. Over two thirds of the population had this index improved at the end of treatment. The TEWL index decreased from the baseline value by 24% and 31% at 2 and 4 weeks, evidencing a recovery of the skin barrier. The improvement was seen in more than three fourths of the population at 4 weeks of treatment.

Finally, to be noted is the clear improvement seen in the quality of life of the patients. The IDQoL index improved significantly already at 14 days of use and continued to increase until the end of treatment.

As limitations to this study, it must be noted that it is an observational investigation that must be confirmed in larger studies. In any case, new data are provided on the viability of applying a 2.1% saline solution spray of seawater to a paediatric population with AD in flare-up phase. This natural product can be an adjuvant treatment in a disease which is highly prevalent in children for which pharmacological options are limited, thus increasing their quality of life.

CONCLUSIONS

A significant improvement was seen in the SCORAD, corneometric and TEWL indices in this pilot study in paediatric patients with mild or moderate flare-ups of AD after twice-a-day application of a 2.1% saline solution spray of seawater for 28 days. Quality of life determined by the IDQoL index improved significantly at the end of treatment.

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To Zurko Research, for the monitoring and analysis of data.

KEY POINTS

THE KNOWLEDGE ON THE MATTER

- Atopic dermatitis (AD) is a chronic inflammatory disease associated with skin hyperreactivity that affects up to 20% of children. The side effects of corticosteroids and antihistamines limit their use in the long term.
- Several authors have shown the protective effects of the water taken from the sea in the prevention and treatment of lesions caused by AD.

WHAT THE STUDY CONTRIBUTES

- Application of a 2.1% saline solution spray of seawater for 28 days in paediatric patient with AD flare-ups improved significantly the SCORAD, corneometric and TEWL indices.
- Quality of life improved significantly.

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