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Clinical Assessment of Treatment Outcomes Following *Borago officinalis* Extract Therapy in Patients Presenting with Cyclical Mastalgia

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Abstract

In order to evaluate the safety and efficacy of *Borago officinalis* (900 mg borage oil capsules) in the treatment of patients presenting with cyclic mastalgia, 91 subjects were included in the study. Efficacy assessments were performed based on data obtained prior to the start of treatment (Pretreatment), and after each menstrual cycle (Assessment 2—following 45 days of treatment; and Assessment 3—at the end of the 90-day treatment period). Primary efficacy measures considered the results of the Mastalgia Questionnaire, including a 100 mm visual analog pain scale assessing mean, most intense mastalgia severity, and impact on work, sleep, and sexual activity. Safety and tolerability measures included any changes in vital signs and physical exam in relation to pretreatment, any changes in clinical laboratory exams in relation to pretreatment, and the occurrence of adverse events after the first dose of study medication. The VAS scores of the mean mastalgia and most severe mastalgia both showed statistically significant ($p < 0.0001$) reductions from Pretreatment to Assessment 3. Mean mastalgia scores improved among 92.3% of the treated patients, while most severe mastalgia scores improved among 93.4% of patients. There were sta-

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tistically significant improvements in the assessments of mastalgia impact on work (χ^2 = 28.24; gl = 4; p < 0.0001), sleep (χ^2 = 14.29; gl = 4; p = 0.0006), and sexual activity (χ^2 = 16.11; gl = 4; p = 0.0029) during the treatment period. The results of this study indicate a significant improvement in the mastalgia of the treated patients together with an improvement in the quality of life parameters evaluated. In terms of safety, the tolerability of the treatment was good, with the presence of some adverse events, all of which had been previously described with use of the *Borago officinalis* extract. No serious side effects were reported, and the events that did occur were transitory. Based on the results of this study, we concluded that the *Borago officinalis* extract was safe and effective in the treatment of cyclic mastalgia among the treated patients.

Keywords

Cyclic Mastalgia, *Borago officinalis*, Borage Oil

1. Introduction

Mastalgia is described as breast tenderness and pain that may be characterized as cyclical, non-cyclical, or extra-mammary. It represents the most common breast symptom reported to general practitioners and is a frequent reason for consultation. Cyclical mastalgia is the most common type of mastalgia, with a reported prevalence of up to one third of all of women of reproductive age [1]-[4]. Though its etiology is unknown, cyclical mastalgia is associated with hormones—especially estrogen—and the menstrual cycle, arising as a result of the breast tissue proliferation coinciding with ovulation, and thus is diagnosed only in women of reproductive age [5]. Non-cyclical mastalgia can occur in both pre- and post-menopausal women, and underlying causes include large breast size, pregnancy, medications, thrombophlebitis, or inflammatory breast cancer. Extra-mammary mastalgia is described as pain referred from other locations such as the chest, spine, or gallbladder and causes include trauma and surgery [6].

Borago officinalis is a plant whose seeds are a rich source of γ-linolenic acid (GLA), an essential fatty acid of the omega-6 series which represents the first product of the n-6 polyunsaturated fatty acid pathway. GLA is believed to possess a number of medicinal attributes, especially anti-inflammatory properties [7]. GLA is converted from linoleic acid (LA) in the human body, and reduced conversion rates result in reduced production of n-6 polyunsaturated fatty acids. The symptoms associated with various conditions, including diabetes, aging, atopic dermatitis, rheumatoid arthritis, alcoholism, cancer, cardiovascular disease, and premenstrual syndrome (PMS), have been associated with reduced production of n-6 polyunsaturated fatty acids. These observations have led to the theory that corroborated in clinical studies, dietary supplementation with GLA which effectively bypasses Δ6-desaturation, effectively alleviates many of these symptoms [8].

In a previous study conducted by our group, *Borago officinalis* extract was found to improve both physical and emotional symptoms of PMS [9]. The aim is to evaluate the use of *Borago officinalis* in the form of borage oil capsules (900 mg) in the treatment of patients presenting with cyclic mastalgia, and to evaluate the efficacy and safety of the use of borage oil in the treatment of cyclic mastalgia in terms of clinical assessments and questionnaires completed by the patient and the investigating physician, physical exam results, and incidence of adverse events, including clinically significant changes in laboratory exams.

2. Material and Methods

Patients presenting PMS and attended at *Hospital das Clínicas de Teresópolis*, *Fundação Educacional Serra dos Órgãos* until May 2012 were selected for the study, following Ethical Committee approval (approval no. 172.079). Included subjects were female patients of reproductive age ($\geq$18 years old) with a previous clinical diagnosis of cyclic mastalgia—defined as breast pain occurring within two weeks of menstruation and relieved by onset of menstrual flow—with a duration $\geq$2 months, with intensity $\geq$30 mm on the Visual Analog Pain Scale. Additionally, inclusion criteria called for treatment with *Borago officinalis* in the form of 900 mg borage oil capsules (standardized to a minimum of 180 mg·GLA/capsule, one capsule per day, commercially available in Brazil as Gamaline V—Herbarium) for 90 days, and who were not pregnant or breastfeeding and using adequate

birth control. Patients presenting non-cyclic mastalgia, hypersensitivity to borage oil, with a medical history of breast cancer, and patients who were pregnant or breastfeeding were excluded from the study.

The clinical research form contained physical exam and clinical laboratory test results obtained from before, during, and at the conclusion of treatment. Efficacy assessments were performed based on data obtained prior to the start of treatment (Pretreatment), and after each menstrual cycle (Assessment 2—following 45 days of treatment; and Assessment 3—at the end of the 90-day treatment period).

The primary efficacy measures considered the results of the Mastalgia Questionnaire, including a 100 mm visual analog pain scale assessing mean and most intense mastalgia severity, ranging from 0 mm or "no pain" on the left side of the scale to 100 mm or "most severe pain" on the right side of the scale. Additionally, the patients assessed the impact of their mastalgia on work, sleep, and sexual activity at each assessment, as "none", "somewhat" and "significant".

Secondary efficacy measures included the Patient and Physician Assessments, in which both the subject and the physician rated the patient's overall condition on a scale of 1 - 10 points, with "1" corresponding to the worse assessment and "10" the best. At Assessment 3, the patient's willingness to continue treatment with the borage oil capsule was also rated on a scale of 1 - 10 points, with "10" corresponding to most willing to continue treatment. At Assessment 3, the study physician also evaluated the overall efficacy of the study medication as "Very Good", "Good", "Fair", or "Poor".

The primary safety and tolerability measures included any changes in vital signs and physical exam in relation to pretreatment, and any changes in clinical laboratory exams in relation to pretreatment, and the occurrence of adverse events after the first dose of study medication. Any laboratory exams out of reference range were recorded as adverse events. Laboratory exams included complete blood count, amylase, glucose, serum prolactin, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, serum potassium, urea, serum creatinine, total and fractionated bilirubins, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), and serum testosterone. The secondary safety measure was the evaluation of overall tolerability of the study medication performed at Assessment 4 by the study physician, using the same classifications of "Very Good", "Good", "Fair", or "Poor" as were used for the overall efficacy assessment.

The clinical research form was filled, coded and the data were analyzed using GraphPad Prism v. 5.1. software. Frequency tables were generated and central tendency measures were calculated (mean, median, mode). As appropriate, we used the Student's T-test or the repeated-measures analysis of variance (ANOVA) for continuous variables and Fisher's test or the χ^2 test for categorical variables. Results were compared between each assessment and throughout the study.

Efficacy endpoints included the percentage of patients with improvement in the Mastalgia Questionnaire, as well as in the individual assessments of pain and functionality. The percentage of patients with Patient and in the Physician's Assessments scores of 8 - 10 at the final Assessment were also efficacy endpoints, along with the percentage of patients receiving an assessment of "Very Good" in the overall assessment of efficacy performed at the study end by the investigating physician.

The safety endpoints for this study included the percentage of patients presenting adverse events, the percentage of patients presenting laboratory alterations, and the percentage of patients receiving an assessment of "Very Good" in the overall assessment of tolerability performed at the study end by the investigating physician.

3. Results

A total of 91 patients were included in the study, in accordance with the protocol. **Table 1** summarizes the demographic and baseline data collected at the start of the study. Contraceptive use was reported among 87 patients, and methods included diaphragm, condom, intrauterine devices, and oral contraceptives. Previous pregnancy was reported among 47 patients. A total of 86 patients (94.51%) reported dysmenorrhea, while 20 (21.98%) patients reported intermenstrual bleeding, and 1 (1.1%) reported amenorrhea. Consumption of coffee, tea, soda, and chocolate was recorded at the Pretreatment Assessment; the results are summarized in **Table 2**.

Mastalgia was reported to be related to the menstrual period among 90/91 patients, with a mean duration of 6.79 (±2.65) years. At the Pretreatment Assessment, the number of days in which the patient experienced mastalgia over the previous month (30 days) was recorded, with a mean of 3.98 (±1.46) days. The majority of the patients (89/91) described bilateral mastalgia, while 1 patient reported pain only in the right breast and one patient only in the left breast. Previous use of mastalgia-directed prescription medication was reported among 62/91

Table 1. Demographic and baseline characteristics.

Observation	Result
Age (years)	27.63 (±) 4.93
Height (cm)	161 (±) 5.75
Ethnicity	
Black	16
Caucasian	36
Mulatto	39
Marital Status	
Divorced	22
Married	45
Single	23
Widowed	1
Dietary habits	
Good	41
Moderate	41
Poor	9
Smoking	
Nonsmoker	34
<10 cigarettes/day	30
≥10 cigarettes/day	27
Alcohol consumption	
None	94
<2 drinks/day	42
≥2 drinks/day	15
Physical exercise	
Regular (at least 1 x/week)	30
Irregular	37
None	24

Data are n or means (±SD).

Table 2. Consumption of coffee, tea, soda, and chocolate at pretreatment.

Consumption	Result (n)	Result (%)
Coffee	10	10.99
Coffee + Tea + Chocolate	3	3.30
Coffee + Tea + Soda + Chocolate	11	12.09
Coffee + Chocolate	12	13.19
Coffee + Soda	7	7.69
Coffee + Soda + Chocolate	17	18.68
Tea	3	3.30
Tea + Chocolate	3	3.30
Tea + Soda	1	1.10
Chocolate	9	9.89
None	1	1.10
Soda	4	4.40
Soda + Chocolate	10	10.99

subjects, while 30/91 subjects reported use of over-the-counter measures.

The VAS scores of the mean mastalgia and most severe mastalgia both showed statistically significant ($p < 0.0001$) reductions from Pretreatment to Assessment 3 (**Figure 1** and **Figure 2**). Mean mastalgia scores improved among 92.3% of the treated patients, while most severe mastalgia scores improved among 93.4% of patients.

There were statistically significant improvements in the assessments of mastalgia impact on work ($\chi^2 = 28.24$; gl = 4; $p < 0.0001$), sleep ($\chi^2 = 14.29$; gl = 4; $p = 0.0006$), and sexual activity ($\chi^2 = 16.11$; gl = 4; $p = 0.0029$) during the treatment period (**Figure 3**).

Table 3 summarizes the results of the physical evaluations performed at each assessment and used as safety measures. There was a statistically significant decrease in weight ($p = 0.0054$) from Pretreatment to Assessment

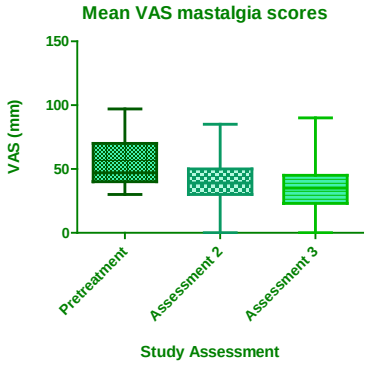


Figure 1. Mean VAS mastalgia scores.

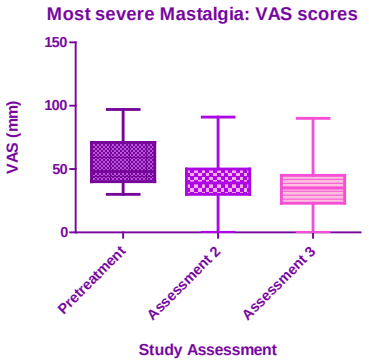


Figure 2. VAS scores of most severe mastalgia.

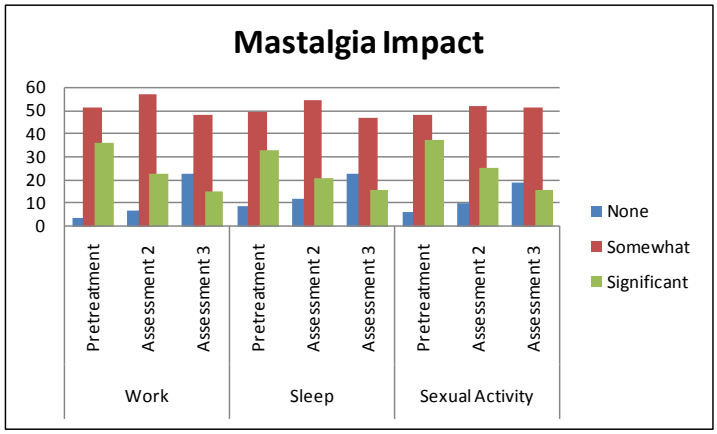


Figure 3. Impact of mastalgia on work, sleep, and sexual activity.

3, although BMI values did not change significantly ($p = 0.063$). Mean systolic blood pressure did not change throughout the study ($p = 0.153$), while there was a decrease in mean diastolic blood pressure ($p = 0.0078$). There was no statistically significant change in heart rate during the treatment period ($p = 0.190$).

There was a statistically significant ($p < 0.0001$) improvement in the scores of the assessment of overall condition performed by the patients and by the study physician (**Figure 4(a)** and **Figure 4(b)**). The physician's assessment of overall efficacy at Assessment 3 was given as "Very Good" for 12 (13.95%) patients, "Good" for 19 (22.09%) patients, "Acceptable" for 42 (48.84%), and "Poor" in 13 (15.21%) patients.

A total of 29 patients presented adverse events (AEs), as summarized in **Table 4**. All of the AEs recorded

Table 3. Safety measures.

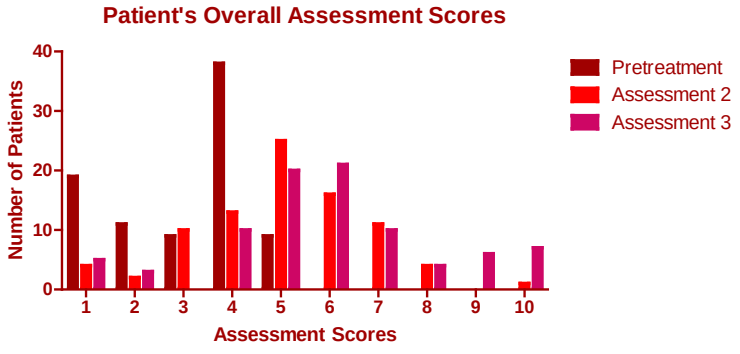
Variable	Pretreatment	Assessment 2	Assessment 3
Weight (kg)	61.45 (±5.58)	61.48 (±5.50)	61.20 (±5.36)
BMI	23.75 (±2.40)	23.80 (±2.42)	23.68 (±2.42)
Systolic BP (mmHg)	119.8 (±6.167)	119.4 (±9.59)	119.3 (±6.54)
Diastolic BP (mmHg)	76.24 (±9.22)	75.33 (±9.67)	75.21 (±9.36)
Heart rate (bpm)	69.43 (±5.08)	68.78 (±4.75)	69.13 (±5.02)

Data are mean (±SD).

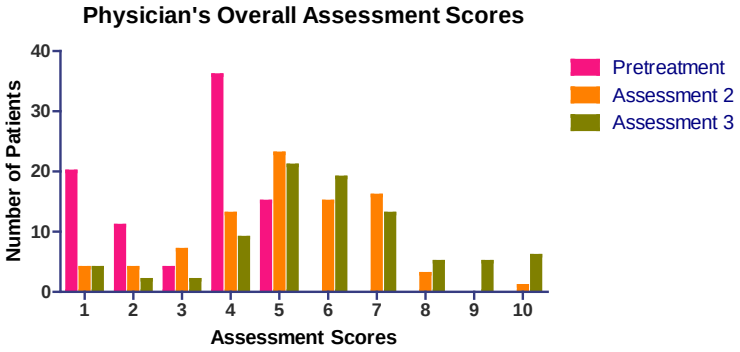
Table 4. Adverse events.

Adverse event	Severity	Number of affected patients
Headache	Moderate	2
	Mild	1
Abdominal cramps	Moderate	1
Abdominal discomfort	Moderate	1
	Mild	1
Diarrhea	Moderate	1
Abdominal distension	Moderate	2
	Mild	1
Epigastric pain	Mild	1
	Moderate	1
Elevated transaminases	Mild	1
Headache	Moderate	1
Eructation	Mild	3
	Moderate	2
Semi-solid feces	Moderate	2
Flatulence	Mild	1
	Moderate	2
Gases	Moderate	1
Meteorism	Moderate	2
	Mild	2
Nausea	Mild	5
	Moderate	2
Pyrosis	Mild	1
	Moderate	1
Vomiting	Moderate	2

Data are n.



(a)



(b)

Figure 4. (a) Scores of the patient's overall assessment; (b) Scores of the physician's overall assessment.

were transitory, mild to moderate in intensity, and none were considered serious. The most common AEs were related to the digestive/gastrointestinal tract, specifically stomach/abdominal upset. In terms of laboratory alterations, one case of elevated transaminases (ALT/AST) was recorded at Assessment 3 (ALT = 55 U/L and ALT = 48 U/L); these exams were within normal range when retested after one week (27 and 32 U/L, respectively; reference ranges ≤33 U/L and ≤32 U/L, respectively). No other alterations in laboratory tests were noted during the treatment period.

Overall tolerability was considered "Very Good" among 28 (32.56%) subjects in the physician's assessment of overall tolerability, while it was considered "Good" in 29 (33.72%) patients, "Acceptable" among 20 (23.26%) patients, and "Poor" in 9 (10.47%) patients.

At the end of the treatment period, subjects who completed the treatment cycle were asked to rate their willingness to continue treatment on a scale of 1 (very unwilling) to 10 (very willing). A total of 30 patients (32.97%) responded with scores of 9 - 10.

4. Discussion

The results of this study indicate a beneficial effect of borage oil in the treatment of cyclical mastalgia. The importance of the impact of mastalgia on day-to-day quality of life is also noted by the high number of patients who had previously turned to prescription or over-the-counter medications to address their mastalgia. The impact of cyclical mastalgia is easily underappreciated, however it does carry a burden of impact on quality of life due to its interference with physical activity, sexual activity, work, and social activity [10] [11]. It is also interesting to note that all but one patient reported consumption of coffee, tea, soda, or chocolate, all of which have been associated with mastalgia, whether on account of caffeine content or presence of methylxanthine [12] [13].

The seeds of the *Borago officinalis* plant yield Borrage oil, an important source of γ-linolenic acid (GLA). GLA is an unsaturated omega-6 fatty acid, which acts as a precursor in prostaglandin synthesis. GLA was experimentally proven to reduce interleukin 1-beta (IL-1beta) production, which may play a role in inflammation and diseases such as rheumatoid arthritis. GLA may also affect cAMP levels which in turn inhibit synthesis of tumor

necrosis factor-alpha, the central inflammatory mediator which also regulates the articular degeneration processes in rheumatoid arthritis [14] [15].

Much of what is known about the therapeutic properties of GLA is based on studies involving evening primrose oil, derived from the seeds of the *Oenothera biennis* plant, which contains a slightly lower GLA concentration in relation to borage oil [16]. A previous meta-analysis of various mastalgia treatments using data collected from randomized clinical trials found no superiority of evening primrose oil over placebo in the treatment of mastalgia [17]. Although our study was uncontrolled, the positive results observed may be due to the higher GLA content of the *Borago officinalis* extract.

The underlying mechanism of action of GLA is believed to result from its downregulation of prostaglandin E2 production, which takes place by a rapid conversion of GLA to dihomo-γ-linolenic acid (DGLA). This conversion increases PGE1 production, and consequently increases intracellular cAMP levels, which in turn inhibits phospholipase, thus limiting the release of arachidonic acid (AA) [18].

GLA and its biosynthesis are crucial to n-6 polyunsaturated fatty acid metabolism. GLA is synthesized in mammals from dietary linoleic acid by the action of Δ6-desaturase, a rate-limiting enzyme. It is then converted to DGLA through the action of a polyunsaturated fatty acid-specific elongase. The enzyme Δ5-desaturase converts DGLA to arachidonic acid, but both DGLA and arachionic acid can be metabolized to form eicosanoids (including prostaglandins). While oxidation of DGLA yields 1-series of prostaglandins by cyclooxygenase, arachidonic acid is converted to 2-series prostaglandins (also by cyclooxygenase) or 4-series leukotrienes (by 5-lipoxygenase). These metabolites are essential in the regulation of many biological activities, and also exert modulatory effects in a variety of diseases. They act in suppression of chronic inflammation, inhibition of platelet aggregation and thrombosis, suppression of vasodilation, lowering of blood pressure, and also inhibit the development of smooth muscle cell proliferation-associated atherosclerotic plaque [8] [16] [18].

With regards to the adverse effects recorded during treatment, the majority of these affected the GI tract, and were mild or moderate in severity. Gamolenic and linoleic acids from evening primrose oil, and presumably similar sources such as borage oil, have been reported to produce minor gastrointestinal disturbances and headache [16] [19]. The laboratory alterations recorded above reference ranges were transitory and none were considered severe. However, long-term dietary supplementation with essential fatty acids should take into account the effect of these compounds on lipid indexes. The adverse events observed in this study were similar to those observed in the previous study of *Borago officinalis* extract [9].

5. Conclusion

The results of this study indicate a significant improvement in the mastalgia of the treated patients together with an improvement in the quality of life parameters evaluated. In terms of safety, the tolerability of the treatment was good, with the presence of some adverse events, all of which had been previously described with use of the *Borago officinalis* extract. No serious side effects were reported, and the events that did occur were transitory. Based on the results of this study, we concluded that the *Borago officinalis* extract was safe and effective in the treatment of cyclic mastalgia among the treated patients.

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Effect of borage oil consumption on fatty acid metabolism, transepidermal water loss and skin parameters in elderly people

Abstract

Human skin is not able to biosynthesize gamma-linolenic acid (GLA, 18:3ω6) from the precursor linoleic acid (LA), or arachidonic acid (AA) from dihomo-gamma-linolenic acid (DHGLA). Dietary supplementation with GLA-rich seed oil of borage skips the step of hepatic 6-desaturation of fatty acids (FA) and, therefore, compensates the lack of these essential FA in conditions with impaired activity of delta 6-desaturase. Twenty-nine healthy elderly people (mean age 68.6 years), received a daily dose of 360 or 720 mg GLA for 2 months, using Borage oil in gelatine capsules (Quintesal®180, manufacturer Galderma Laboratorium GmbH, Freiburg, Germany). The effects of fatty acids derived from ingested borage oil capsules on skin barrier function were assessed by measurement of transepidermal water loss (TEWL). The consumption of borage oil induced a statistically significant improvement of cutaneous barrier function in the elderly people, as reflected in a mean decrease of 10.8% in the transepidermal water loss. Thirty-four percent of the people noted itch before borage oil consumption and 0% afterwards. Dry skin was claimed to be reduced from 42 to 14%, but no significant alteration of skin hydration was measured. The FA-composition of erythrocyte membrane phospholipids demonstrated an increase of GLA (+70%) and DHGLA (+18%) and a reduction of saturated and monounsaturated FA. There was no significant alteration in nervonic

acid or in AA content, but an increase in the DHGLA/AA ratio (+23%). Thus, the consumption of borage oil by elderly people lead to alteration of FA metabolism and improved skin function.

Introduction

Physiologic aging processes and the accumulation of exogenously induced damages cause age associated alterations of the skin. As a consequence, skin homeostasis in old age is disturbed. Even in healthy elderly people dry skin and itch are observed frequently. Aging is one of the factors proposed to attenuate the activity of the delta 6 fatty acid desaturase. This reduced activity to desaturate, e.g. linoleic acid (LA, 18:2ω6) to gamma-linolenic acid (GLA, 18:3ω6) was claimed to contribute to skin alterations observed in old age (Horrobin, 1989). Human skin is not able to biosynthesize GLA from the precursor LA, or arachidonic acid (AA, 20:4ω6) from dihomo-gamma-linolenic acid (DHGLA, 20:3ω6), because of lacking enzymes delta 6- and delta 5-desaturase (Chapkin and Ziboh, 1984, Chapkin et al., 1986). Therefore, metabolites of essential fatty acids (EFA) have to be synthesized in the liver and transported to the skin by the blood stream. Dietary supplementation with GLA-containing oils skips the metabolic step of 6-desaturation of LA to form GLA. Such a supplementation should compensate the lack of EFA in cases and in conditions with impaired activity of delta 6-desaturase, like in diabetes mellitus, atopic eczema or in normal aging (Brenner, 1982, Horrobin, 1983, Brenner, 1989). Since the seed oil of borago officinalis is rich in gamma-linolenic acid (GLA; up to 25% of total fatty acids), we used it to explore the influence of dietary supplementation in 29 healthy elderly people on skin barrier function, skin water content and on fatty acid metabolism as reflected in the erythrocyte membranes. The observed reduction of the transepidermal water loss (TEWL) indicates an improved cutaneous barrier function induced by 8 weeks of borage oil consumption. In addition, the volunteers reported improvement of itch. Skin dryness was not altered significantly. As expected, portions of GLA and DHGLA in the erythrocyte membrane phospholipid fatty acid pattern were increased significantly.

Study design

In an open study 29 free living, apparently healthy elderly people, showing no signs of skin diseases, received a daily dose of 360 or 720 mg GLA for 2 months. The mean age of the 13 men and 16 women was 68.6±7.6 years (range: 54.4–84.5 years). Borage oil was applied using soft gelatine capsules (Quintesal®180, manufacturer Galderma Laboratorium GmbH, Freiburg, Germany). One capsule contains 0.75 g±7.5% of borage oil with a GLA portion of 175 mg±7.5%. In addition 20 mg±7.5% of vitamin E

Results

During the 2 months of dietary borage oil supplementation the barrier function of skin improved by 10.8% (mean), according to a reduction of TEWL values from 7.65±2.96 to 7.20±2.58 and finally to 6.82±2.29 g/m$_2$ h (mean, $P<0.05$; see Fig. 1). In addition, the water content of the stratum corneum increased slightly from 66.17±9.91 to 68.76±11.58 and finally to 69.10±13.61 units (mean; statistically not significant; see Fig. 2). Ten out of 29 people said to suffer from itch before supplementation,

Discussion

The outermost layer of the skin, stratum corneum, provides a barrier against the external environment and is responsible for skin impermeability for most agents. Reports on the physiological alterations of the barrier function of the stratum corneum in old age are sparse. A tendency to slightly increased TEWL measurements in older people indicates a decreased barrier function in old age (Raab and Kindl, 1991, Berardesca, 1993, Klein et al., 1993). The role of fatty acids in the skin has been

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Borage oil in the treatment of atopic dermatitis

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Abstract

Nutritional supplementation with omega-6 essential fatty acids (ω-6 EFAs) is of potential interest in the treatment of atopic dermatitis. EFAs play a vital role in skin structure and physiology. EFA deficiency replicates the symptoms of atopic dermatitis, and patients with atopic dermatitis have been reported to have imbalances in EFA levels. Although direct proof is lacking, it has been hypothesized that patients with atopic dermatitis have impaired activity of the delta-6 desaturase enzyme, affecting metabolism of linoleic acid to gamma-linolenic acid (GLA). However, to date, studies of EFA supplementation in atopic dermatitis, most commonly using evening primrose oil, have produced conflicting results. Borage oil is of interest because it contains two to three times more GLA than evening primrose oil. This review identified 12 clinical trials of oral or topical borage oil for treatment of atopic dermatitis and one preventive trial. All studies were controlled and most

were randomized and double-blind, but many were small and had other methodological limitations. The results of studies of borage oil for the treatment of atopic dermatitis were highly variable, with the effect reported to be significant in five studies, insignificant in five studies, and mixed in two studies. Borage oil given to at-risk neonates did not prevent development of atopic dermatitis. However, the majority of studies showed at least a small degree of efficacy or were not able to exclude the possibility that the oil produces a small benefit. Overall, the data suggest that nutritional supplementation with borage oil is unlikely to have a major clinical effect but may be useful in some individual patients with less severe atopic dermatitis who are seeking an alternative treatment. Which patients are likely to respond cannot yet be identified. Borage oil is well tolerated in the short term but no long-term tolerability data are available.

Introduction

Atopic dermatitis (atopic eczema) is a chronic-relapsing inflammatory skin condition that can be distressing and, when severe, can be functionally and socially disabling [1]. It affects up to 15–20% of children in developed countries, and the incidence is increasing [2], [3]. The condition improves or resolves with age in most patients. However, many patients will require intermittent treatment for exacerbations through to early adulthood or beyond with agents such as topical corticosteroids that have significant adverse effects (Table 1) [2], [3], [4].

The pathogenesis of atopic dermatitis is multifactorial and involves a complex interaction between environmental, immunological, and genetic factors [1], [5]. It is associated with hyperreactivity to environmental triggers. T-cell-mediated processes and various cytokines and chemokines play an essential role. Most, but not all, cases are IgE-mediated. Atopic dermatitis often co-occurs with other atopic conditions such as asthma and hayfever. The condition has been linked to various regulatory genes, and it is strongly linked to a family history of atopy. The pathophysiology of

atopic dermatitis includes skin barrier defects causing increased transepidermal water loss (TEWL) and increased permeability to irritants and allergens. There is increased susceptibility to infection, and colonization of the skin with *Staphylococcus aureus* contributes to inflammation of the skin.

It has been proposed that atopic dermatitis is associated with an abnormality in essential fatty acid (EFA) metabolism, in particular, affecting production of gamma-linolenic acid (GLA), and possibly also impaired incorporation of EFAs into membrane phospholipids [6], [7], [8]. In the body, EFAs and their products, particularly those of the omega-6 (ω-6) series, are important for skin structure and physiology. EFAs play a crucial role in cell membrane fluidity and flexibility and affect activity of membrane-associated proteins such as receptors and enzymes. Notably, EFAs are key components in the membrane systems that maintain the structural integrity of the skin and epidermal function as a permeability barrier. Furthermore, EFAs are metabolized to highly active eicosanoid products, such as prostaglandins and leukotrienes, that modulate inflammatory, immunologic, and proliferative responses including those of the skin cells [6], [8], [9], [10].

In states of EFA deficiency, skin changes similar to those of atopic dermatitis are replicated [6], [8]. The skin becomes inflamed with dry, scaly, red, and weeping lesions. There is an increased rate of proliferation of epidermal cells, metabolic activity, and formation of sterol esters and abnormal keratinocytes. The skin's normal function as a barrier to water loss becomes markedly impaired [6], [8]. There is increased colonization with *S. aureus* [11]. This atopic dermatitis-like skin disorder is reversed by treatment with ω-6 EFAs [9].

There remains controversy over the exact importance of EFA disturbances as a pathophysiological factor in atopic dermatitis, and current data fall short of direct proof. Nevertheless, the finding that EFA abnormalities can be detected prior to the development of atopic dermatitis does support a causative role [12]. EFA

abnormalities could contribute to atopic dermatitis in two ways: first, through a direct effect on the skin structure and function, and, second, by affecting maturation and sensitization of the immune system affecting the skin [6]. The abnormalities in EFA metabolism could potentially reduce levels of the prostaglandin PGE_1, resulting in reduced levels of cyclic AMP, and thereby affecting parts of the immune system causing selective hyperactivity.

Such data have stimulated interest in whether EFA-containing oils, particularly oils such as evening primrose oil that are rich in the ω-6 EFAs, are of value in the treatment of atopic dermatitis. More recently, borage oil (also known as starflower oil) has become of interest because of its high GLA content, which is two to three times higher than that of evening primrose oil [13], [14].

While there have been a number of reviews on the use of evening primrose oil in atopic dermatitis, there have been very few, if any, comprehensive reviews focused solely on borage oil. One meta-analysis [15] considered all types of EFA supplementation including borage oil but was published several years ago and does not include more recent important data. The aim of this article is to outline the rationale behind the interest in the potential use of borage oil in atopic dermatitis and to review the clinical data on its use in this indication. This review focuses only on data relating to borage oil specifically. Studies testing GLA alone or other GLA-containing oils may not be applicable to borage oil because activity of different GLA-containing oils is potentially affected not only by the GLA content but also by the position of the GLA on the triglyceride and the balance between ω-6, ω-3, ω-9, and other fatty acids present in the oil

Section snippets

Rationale for borage oil supplementation in atopic dermatitis

Borage oil contains high levels of the ω-6 series EFAs that are particularly important in skin structure and function, among other functions [8]. Borage oil does not contain significant amounts of the ω-3 series EFAs; while the ω-3 EFAs have some role in maintaining skin health, they are more important for neuronal development and are of particular importance in the retina, brain, and cardiovascular systems [16].

Within the body, the ω-6 series of EFAs derives from linoleic acid, which is

Efficacy of borage oil in atopic dermatitis

A literature search not limited by date or language identified 11 clinical trials of oral borage oil [17], [29], [40], [41], [47], [48], [49], [50], [51], [52], [53] and one clinical trial of topical borage oil [54] for treatment of atopic dermatitis. Additionally, a study of preventive use of borage oil supplementation in neonates at risk of developing atopic dermatitis was included [18]. All studies that assessed clinical outcomes with use of borage oil for either treatment or prevention of

Discussion

The mainstay of treatment of atopic dermatitis is the use of emollients and avoiding aggravating factors, but acute exacerbations can require treatment with topical corticosteroids or possibly other immunomodulators [2], [3], [4]. As outlined in Table 1, existing treatment options have various limitations, including significant adverse effects.

There is a proposed pathophysiological basis to support the concept of ω-6 EFA supplementation in the treatment of atopic dermatitis. EFAs play a vital

Conclusions

The current review identified 11 clinical trials of oral borage oil and one trial of topical borage oil for the treatment of atopic dermatitis, and a further trial of borage oil for prevention of atopic dermatitis in at-risk neonates. Although controlled and usually double-blind and randomized, many of the studies had significant methodological limitations particularly in regards to small patient numbers and heterogeneous and poorly defined patient populations. Possibly in part as a consequence

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