

Efficacy and tolerability of borage oil in adults and children with atopic eczema: randomised, double blind, placebo controlled, parallel group trial

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Abstract

Objective To study the efficacy and tolerability of borage oil, which contains a high concentration of γ linolenic acid, in children and adults with atopic eczema.

Design Single centre, randomised, double blind, placebo controlled, parallel group trial.

Setting Acute district general hospital in Nuneaton, England.

Participants 151 patients, of whom 11 failed to return for assessment, leaving an evaluable population of 140 (including 69 children).

Intervention Adults received four capsules of borage oil twice daily (920 mg γ linolenic acid), and children received two capsules twice daily, for 12 weeks.

Main outcome measures Change in total sign score at 12 weeks measured with the six area, six sign, atopic dermatitis (SASSAD) score (primary endpoint); symptom scores, assessed on visual analogue scales; topical corticosteroid requirement, assessed on a five point scale; global assessment of response by participants; adverse events and tolerability.

Results The mean SASSAD score fell from 30 to 27 in the borage oil group and from 28 to 23 in the placebo group. The difference between the mean improvements in the two groups was 1.4 (95% confidence interval -2.2 to 5.0) points in favour of placebo ($P=0.45$). No significant differences occurred between treatment groups in the other assessments. Subset analysis of adults and children did not indicate any difference in response. The treatments were well tolerated.

Conclusion γ linolenic acid is not beneficial in atopic dermatitis.

Introduction

Essential fatty acids are long chain fatty acids that are needed for normal cutaneous function and cannot be synthesised by human metabolism. Most important are the n6 series fatty acids, which include γ linolenic acid, and the n3 series, which include eicosapentaenoic acid. Many mechanisms have been proposed whereby supplementation with essential fatty acids might prove effective in treating atopic dermatitis.¹ For example,

atopic eczema has been suggested to result partly from defective conversion of linoleic acid to metabolites such as the anti-inflammatory prostaglandin E_1 .^{1,2} This disease might therefore respond to fatty acid supplementation, which would bypass this metabolic step.

The most investigated form of supplementation has been with γ linolenic acid.³⁻⁸ Although this treatment has consistently proved safe and well tolerated, efficacy has been inconsistent.⁹ One possible explanation for the inconsistent results may be that the dose used has been too low in some trials. Purified borage oil contains a minimum of 23% γ linolenic acid. Borage oil is used to fortify infant foodstuffs with essential fatty acid and is available over the counter in chemists and in health food shops, where it is sold as "starflower oil."

Only one large well reported randomised controlled trial of borage oil in atopic eczema has been published.¹⁰ A response to borage oil could not be confirmed for the overall population with the primary response criterion, the quantity of topical steroid required to achieve a 50% reduction in the Costa severity score. Four smaller studies have been reported, two suggesting an improvement and two suggesting none.¹¹ We report here a further trial investigating the efficacy and tolerability of borage oil in the treatment of atopic eczema in both adults and children.

Methods

Design

The study was a prospective, randomised, double blind, placebo controlled trial of parallel group design, done in a single centre. We assessed participants at baseline and at 2, 4, 8, and 12 weeks.

Participants and treatment

We recruited patients aged over 2 years attending our department for treatment of atopic dermatitis diagnosed by using conventional criteria.¹² Borage oil and placebo treatments were provided in matching capsules. Adults received four 500 mg capsules twice daily, providing 920 mg of γ linolenic acid for those receiving borage oil. Children received half this dose. We allowed patients to use conventional treatment for atopic eczema throughout the study. We permitted no



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Table 1 Mean (SD) SASSAD scores, symptom scores, and topical steroid requirement and differences between treatment groups at the end of treatment

	Borage oil (n=85)		Placebo (n=55)		Difference (95% CI) at end of treatment
	Baseline	End of treatment	Baseline	End of treatment	
SASSAD	30 (16)	27 (17)	28 (14)	23 (16)	3.6 (-2.1 to 9.3)
Pruritus	50 (24)	42 (28)	56 (24)	42 (30)	-0.46 (-10.3 to 9.4)
Sleep disturbance	30 (25)	28 (27)	44 (28)	33 (30)	-5.3 (-14.9 to 4.3)
Irritability	40 (29)	35 (27)	45 (27)	34 (31)	0.87 (-8.9 to 10.7)
Topical steroid requirement	3.4	3.2	3.7	3.3	0.1

SASSAD=six area, six sign, atopic dermatitis.

changes in concomitant treatment for two weeks before the study or for the duration of the study, except in the quantity and frequency of topical steroid application, which could be adjusted as needed in relation to the severity of the disease.

Assessments

We assessed disease activity objectively at each visit by using the six area, six sign, atopic dermatitis (SASSAD) score.¹³ This scoring system involves assessment of six signs (erythema, exudation, excoriation, dryness, cracking, and lichenification) at six sites (hands, feet, arms, legs, head and neck, and trunk). Each sign is graded at each site on a four point scale (0-3, representing grades of none, mild, moderate, and severe). The maximum score theoretically possible is therefore 108.

To assess the severity of symptoms, patients used horizontal 10 cm visual analogue scales marked none at the left hand end and worst ever at the right. We assessed itching, sleep disturbance, and irritability in this way. Participants made an overall assessment of response to treatment at the end of the treatment relative to the baseline, on a five point scale: worse, same, improved, much improved, or cleared. These assessments were also done on discontinuation of treatment in patients who were withdrawn. We recorded the need for topical steroid at each visit by using a five point scale: none, occasionally, alternate days, once daily, twice daily. Participants assessed overall tolerability of the treatment on a four point scale: very good, good, fair, or poor.

Sample size

The study was designed to have 80% power to detect a treatment response of 20% (that is, above the response to placebo), with a standard deviation (derived from existing data) of 35%, at a significance level of 0.05. We estimated that 120 participants would be needed. We anticipated that around 20% of participants would be withdrawn and therefore aimed to recruit 152 participants, comprising 76 adults and 76 children.

Results

Demographics

We recruited 151 participants between February 1997 and July 2001. Only two patients (both in the placebo arm) were withdrawn owing to adverse events—one developed a blotchy erythematous rash; the other developed diarrhoea and vomiting, headache, fever, and worsening of asthma. Disease severity was comparable in the two groups at baseline (table 1).

Efficacy

Table 1 and figure 1 show mean SASSAD scores and symptom scores. The mean SASSAD score fell from 30 to 27 in the borage oil group and from 28 to 23 in the

placebo group at the end of treatment. The difference between the mean improvements in the two groups was 1.4 (95% confidence interval -2.2 to 5.0) points, with a marginally greater improvement in the placebo group (P = 0.45).

Symptom scores all fell in both treatment groups during the study (table 1). Pruritus, sleep disturbance, and irritability all improved slightly more in the placebo group than in the borage oil group. These differences between the two groups were not significant for any of the symptoms. Table 2 shows patients' assessments of overall response to treatment. Table 1 and figure 2 show data on the frequency of application of topical corticosteroids at baseline and throughout the study. Subset analysis of adults and children yielded no suggestion of any difference between them in any of the parameters studied.

Tolerability

Both treatments were generally well tolerated (tables 3 and 4).

Discussion

The greatest level of response to borage oil likely to be compatible with these data is a two point improvement in the SASSAD score. If a benefit of this magnitude

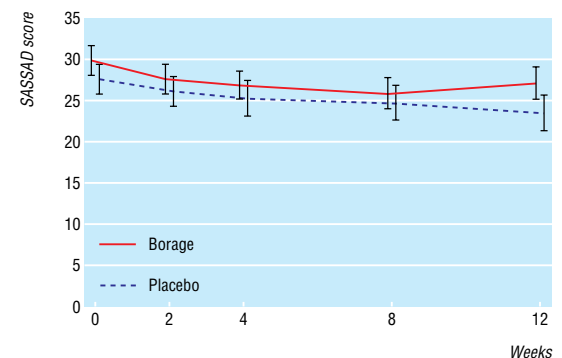


Fig 1 Six area, six sign, atopic dermatitis (SASSAD) scores throughout the trial (n=140; error bars show SE)

Table 2 Overall assessments of response. Values are numbers (percentages)

	Borage oil (n=81)	Placebo (n=52)
Worse	15 (19)	6 (12)
Same	28 (35)	20 (39)
Improved	26 (32)	14 (27)
Much improved	11 (14)	11 (21)
Cleared	1 (1)	1 (2)

P=0.28, χ^2 test for trend; data not recorded for seven participants.

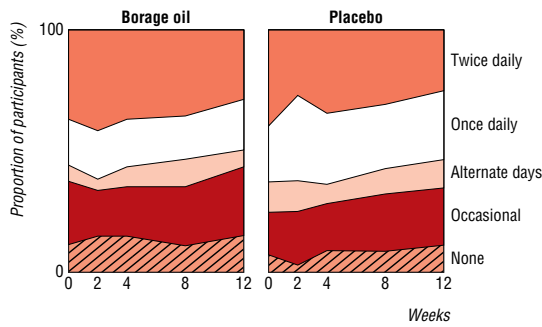


Fig 2 Use of topical steroids assessed at each visit on a five point scale (n=140)

occurred (approximately 7% of the baseline sign score), this would be of limited clinical value. A two point improvement might represent, for example, an improvement of a single sign by one grade in two areas or of two different signs in one out of the six areas assessed. However, the data do not exclude the possibility of such a small degree of benefit. The data do not suggest that a longer duration of treatment would have been more likely to have yielded a positive outcome. Indeed, figure 1 would suggest that, if anything, the difference in favour of placebo was widening.

The design and method of this trial worked well. The narrow confidence intervals for the improvement in sign score indicate that the sample size was correctly estimated and that the study was adequately powered.

These data are compatible with results from the largest studies in which evening primrose oil was used as a supplement of γ linolenic acid.^{7 8} The results are also compatible with the results of previous trials on supplementation with borage oil.^{10 11} The dose of γ linolenic acid administered in this study was the highest used in any trial to date. The results would therefore seem to refute any contention that the response is dose related or that the lack of response, or the inconsistent

Table 3 Patients' assessment of tolerability of treatment. Values are numbers (percentages)

	Borage oil (n=81)	Placebo (n=52)
Very good	32 (40)	22 (42)
Good	37 (46)	25 (48)
Fair	10 (12)	5 (10)
Poor	2 (3)	0

P=0.41, χ^2 test for trend; data not recorded for seven participants.

Table 4 Adverse events reported by more than one participant: number (percentage) of participants reporting

Event	Borage oil (n=85)	Placebo (n=55)
Upper respiratory tract infection	22 (26)	21 (38)
Diarrhoea	6 (7)	6 (11)
Nausea, vomiting, or both	3 (4)	5 (9)
Abdominal pain	5 (6)	2 (4)
Episodes of asthma	1 (1)	4 (7)
Episodes of allergic rhinitis	1 (1)	1 (2)
Episodes of urticaria	2 (2)	1 (2)
New rash	0	2 (4)
Musculoskeletal pains	3 (4)	3 (6)
Skin sepsis	6 (7)	7 (13)
Glandular fever	2 (2)	0
Headache	1 (1)	4 (7)

What is already known on this topic

The essential fatty acid γ linolenic acid has been investigated in many small trials as a supplementary treatment for atopic eczema

Results have so far been conflicting and inconclusive, but some studies have suggested a dose related benefit

What this study adds

The dose of γ linolenic acid in this study was the highest so far investigated

The symptoms and signs of atopic dermatitis improved to a similar degree in both groups, with the minimal difference being in favour of placebo

This study was well powered and confidence intervals were narrow, so γ linolenic acid is unlikely to offer any useful benefit in treatment of atopic dermatitis

response, seen in some previous trials has resulted from the dose being too low in those trials.

We found no evidence of a steroid sparing effect from borage oil treatment. The recording of topical steroid requirement has always been one of the most difficult aspects of trials on atopic dermatitis, but the five point scale used in this study proved useful and simple to apply. The result seems incompatible with the 60% reduction in steroid requirement reported in a previous small study on evening primrose oil.⁴

In conclusion, it seems unlikely that dietary supplementation with γ linolenic acid is beneficial in management of atopic dermatitis.

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