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To cite this article: John Berth-Jones, Ian Pollock, Ross M. R. Hearn, Sue Lewis-Jones, Mark Goodfield, Christopher E. M. Griffiths, Ram Gulati, Pamela McHenry, Anthony Abdullah, Jennifer Ott, Andrew Wright, Benjamin Walker, Michael T. Stevens & Alan M. Edwards (2015) A randomised, controlled trial of a 4% cutaneous emulsion of sodium cromoglicate in treatment of atopic dermatitis in children, *Journal of Dermatological Treatment*, 26:3, 291-296, DOI: [10.3109/09546634.2014.946380](https://doi.org/10.3109/09546634.2014.946380)

To link to this article: <https://doi.org/10.3109/09546634.2014.946380>



Accepted author version posted online: 18 Jul 2014.
Published online: 07 Aug 2014.



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ORIGINAL ARTICLE

A randomised, controlled trial of a 4% cutaneous emulsion of sodium cromoglicate in treatment of atopic dermatitis in children

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic inflammatory skin disease. Sodium cromoglicate (SCG) is a chromone with anti-inflammatory, anti-itch and anti-allergic activity. This trial is a 12-week comparison (RCT) of a 4% SCG cutaneous emulsion with its vehicle in AD. **Materials and methods:** 208 children aged 2–12 years participated, 104 in each group. The primary endpoint was change in SCORAD score. Secondary endpoints included SASSAD score, topical steroid usage and global assessments.

Results: SCORAD was reduced by 28% (SCG group) and by 19% (vehicle); difference was statistically significant ($p=0.03$) after 8 weeks and nearly significant ($p=0.09$) after 12. A similar result occurred in SASSAD ($p=0.001$ at 8 weeks). In subjects without major protocol deviations (SCG-64, vehicle-63), difference in SCORAD remained significant at 12 weeks ($p=0.04$). Weight of topical steroids reduced in both groups: -0.60 ± 1.3 g/day (35%), SCG and -0.05 ± 1.1 g/day vehicle ($p=0.04$). Treatment success, defined as investigator global opinion graded very or moderately effective, was significantly more frequent in SCG group ($p=0.025$). Application site discomfort reported by 12.5% of subjects in SCG group and 16.5% in vehicle group.

Conclusions: SCG 4% cutaneous emulsion provides an effective, well-tolerated, steroid-sparing treatment for AD in children.

Keywords

Children, clinical trial, cromolyn, eczema, long term, topical

History

Received 6 May 2014

Revised 15 July 2014

Accepted 15 July 2014

Published online 7 August 2014

Introduction

Atopic dermatitis (AD), an inflammatory skin disorder, affects up to 10% of the paediatric population. Current treatment consists of emollients to which are added topical corticosteroids. Topical steroids cause concern over cutaneous and systemic adverse effects. An additional anti-inflammatory treatment without the disadvantages of steroids, and with a steroid-sparing effect, would represent a significant step forward.

Sodium cromoglicate (SCG), a chromone, has anti-allergic, anti-pruritic and anti-inflammatory properties. Its primary mode of action is to inhibit the release of inflammatory mediators from sensitised mast cells (1). It also modifies the activity of sensory nerves that have a direct effect on itching of the skin (2,3).

Topical applications of SCG used previously for AD have failed to show consistent efficacy (4–13). The 4% SCG cutaneous

emulsion (4% SCG emulsion) used in this trial was designed to provide improved penetration of the aqueous solution through skin and to provide a protective skin barrier.

Two previous trials in children with AD compared the 4% SCG emulsion with the vehicle in which SCG is dissolved, using the change in SCORAD score as the primary outcome measure (14,15). The first (14) included 114 children, aged 2 to 12 years. Mean SCORAD scores were reduced by 14.0 ± 11.34 in the 4% SCG emulsion group and 8.2 ± 13.76 in the vehicle group. The difference was statistically significant, $p=0.018$. The second (15) included 177 subjects; mean SCORAD scores were reduced by 15.34 ± 17.09 (4% SCG emulsion) and by 18.04 ± 17.86 (vehicle). The difference was not significant. After the 12-week RCT, treatment continued for 12 months on known 4% SCG emulsion. At the end of this open period, the SCORAD score was reduced by 20.41 ± 18.42 , an overall reduction of 56%.

Subjects in the second trial had greater severity of skin dryness than those in the first trial, which would tend to exaggerate any emollient effect. The vehicle used in these trials is a very effective emollient.

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In this third trial, the protocol was similar to that of the first trial, apart from all subjects using an adequate emollient for 4 weeks prior to randomisation to reduce skin dryness.

The objective of this study was to evaluate the efficacy and safety of topically applied 4% SCG cutaneous emulsion in AD in children and to examine the potential to spare the usage of topical steroid.

Methods

A multi-centre, randomised, double-blind, parallel group study was conducted in specialist hospital departments and clinical trial research units.

Treatments

After screening, subjects were initially observed over a 4-week ‘‘baseline period’’ using their existing treatment of emollients, topical steroids and anti-histamines (if used previously). Then, in addition, subjects were given test treatments with 4% SCG emulsion or vehicle for 12 weeks.

Subjects were continued with existing treatments of emollients and topical steroids throughout the trial, but were allowed to reduce the amount of both if the severity of the disease allowed. If it was deemed necessary to change the topical steroid being used, the subject was withdrawn from the trial.

Subjects

Participants were children with AD according to the criteria of the UK Working Party for Diagnostic Criteria for Atopic Dermatitis (16), aged between 2 and 12 years. Inclusion criteria required a SCORAD score of ≥ 25 and ≤ 60 at screening and randomisation and diary card scores for overall skin condition and itch ≥ 2 on at least 4 days of the last 14 days of the baseline period.

Assessments

The primary outcome measure was the change in SCORAD score (17,18). This was recorded at the screening visit, after 2 and 4 weeks during the baseline and after 2, 4, 8, and 12 weeks on test treatment.

Additional outcome measures were as follows:

- (1) Change in SASSAD score (19) was assessed at the same time points as the SCORAD score.
- (2) Daily diary card scores of overall skin condition, itch and sleep disturbance were each recorded by parents/patients using 4-point severity scales.
- (3) QOL assessments using Children’s Dermatology Life Quality Index (CDLQI) (20) were done for children aged 5 to 12 years and Infants’ Dermatitis Quality of Life Index (IDQOL) (21) for children aged 2–4 years.
- (4) The number of times topical steroid was applied and the steroid container weight were recorded daily.
- (5) Weights of emollient and test treatment containers were recorded daily.
- (6) Global opinions of effectiveness and acceptability. At visit 7 or at early withdrawal, both parent and investigator rated the effectiveness of test treatments using a 5-point scale.

Statistical analysis

The sample size was determined using a pooled estimate of the residual standard deviation of the change from baseline of the SCORAD score in the two previous trials with this formulation (14). In order to provide 90% power to detect a difference between treatments of 7 units, using a two-sided alpha of 0.05, a sample

size of 90 subjects in each group (total 180) was required. To allow for drop-outs 200 subjects were recruited.

Patient numbers were allocated at visit 3 (randomisation), determined by a computerised schedule provided by the CRO organisation, which monitored the study.

Subjects, parents and investigators were all blinded to the treatment allocation.

The primary endpoint was the change in SCORAD score using the full analysis set (FAS intention-to-treat analysis). The two treatments were compared at each visit using an analysis of covariance with treatment and centre grouping as factors and baseline as a covariate, with the adjusted least square mean difference between treatments and 95% confidence intervals provided. The changes from baseline for all secondary outcomes were analysed at each visit using an analysis of covariance model as described for the primary variable. A last-observation-carried-forward (LOCF) approach was used for any missing values. Diary card symptom scores, topical steroid used, emollient and test treatment use were summarised for each 2-week period and the change from the last 2 weeks of the baseline was analysed using an analysis of covariance as described for the primary variable. At a blinded review meeting held before the randomisation code was broken, a per protocol set (PPS) was defined excluding subjects with major protocol deviations. Details of the FAS and PPS and the reasons for exclusion are provided in Figure 1.

The Shapiro–Wilk test was used to test the normal assumption and normal Q–Q plot prepared to check for any departure from the linearity of the plotted points, which indicated a departure from normality.

Global opinions of efficacy of the parent and investigator were dichotomised into those showing improvement (very effective/moderately effective) and those not (slightly effective/no effect/made condition worse) as per previous studies, and the two groups were compared using a Cochran–Mantel–Haenszel test adjusting for centre grouping. Subjects withdrawn due to lack of efficacy and who did not have an opinion were included as the worst case on the scale.

Ethical considerations

The protocol was approved by a registered Ethics Committee and conducted in accordance with the Declaration of Helsinki. The protocol was pre-registered on a clinical trial database, number ISTRN 02084571.

Parents gave informed consent and children, where appropriate, assent to the trial.

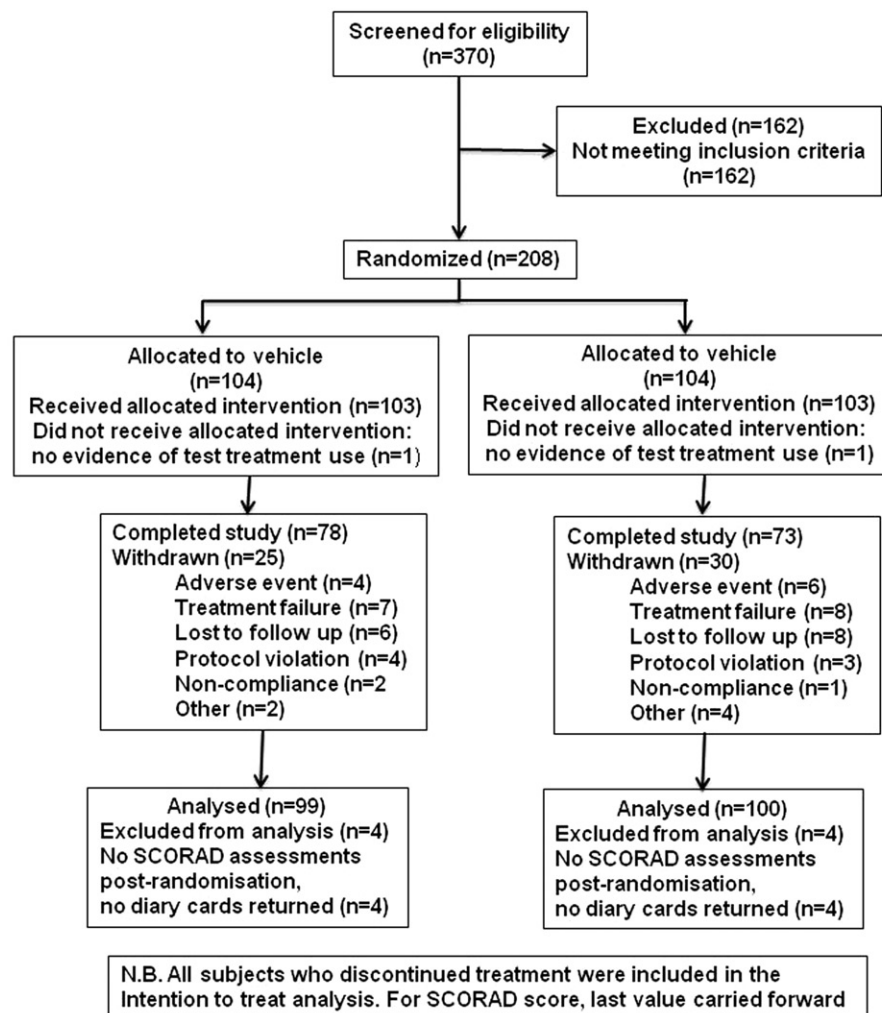
Results

Demographic characteristics of subjects and baseline values for the outcome measures were entered (Table 1); a flow chart providing details of numbers analysed in the full analysis and per protocol sets (Figure 1). Recruitment was started in March 2009, and the last subject completed the study in May 2012.

Efficacy results are presented as change from the baseline values at visit 3 (baseline) to those at visit 7 (12 weeks of randomised treatment) or the mean daily values for weeks 3–4 to weeks 15–16 (Tables 2–5).

All outcome measures showed consistent intra-group, highly significant improvements compared to baseline values. For the change in SCORAD score, a statistically significant difference between treatments was seen at visit 6 (8 weeks) in the FAS ($p=0.0249$) and just failed to achieve significance at visit 7 (12 weeks) ($p=0.0884$) (Table 2). For the PP set statistically significant differences between treatments occurred at visit 6 ($p=0.0303$) and at visit 7 ($p=0.0436$) (Table 3).

Figure 1. Flow diagram.



During the baseline the SCORAD score did not change significantly.

The changes in the SASSAD score (Table 4) showed significant differences between treatments at visit 4 ($p = 0.0381$) and at visit 6 ($p = 0.0014$) but not at visit 7 ($p = 0.2592$).

Diary scores for overall skin condition, itch, and sleep disturbance all showed significant improvement compared to baseline, but in no case was the difference between treatments significant.

Use of concomitant therapy

During the baseline, subjects continued their existing therapy. All 199 subjects were treated with emollients and 171 with topical steroids of varying potency in addition. Details of concomitant therapy are given in Table 5. All subjects were continued with emollients and topical steroids throughout the trial, but the amount used each day was reduced if disease severity allowed.

The mean $\pm$ SD number of steroid applications used per day was reduced from 1.20 ± 0.605 to 0.96 ± 0.645 in the 4% SCG group and from 1.06 ± 0.612 to 0.96 ± 0.672 in the vehicle group. The proportion of days used was reduced from 76% to 56% in the 4% SCG group and from 70% to 63% in the vehicle group. In neither case was the treatment difference significant.

The mean weight of topical steroids used daily was reduced in both groups, the difference being statistically significant in favour of 4% SCG from weeks 11–12 to weeks 15–16 (Table 6).

Quality of life

The mean CDLQI was reduced by -3.2 ± 5.68 in the 4% SCG emulsion group and by -2.5 ± 4.89 in the vehicle group. The equivalent changes in the IDQOL were -2.7 ± 4.30 and -1.7 ± 4.52 , respectively. In neither case was the difference between treatments significant.

Global opinion of efficacy

Both parents and investigators thought the effectiveness of the 4% SCG emulsion to be statistically significantly better than the vehicle. (Table 7).

Treatment success

Treatment success was defined as the percent of subjects in whom the investigator reported the treatment to be very or moderately effective. These figures are 69% for the 4% SCG emulsion compared to 52% for the vehicle: Odds ratio (95% CI) 1.31 (1.04; 1.67); $p = 0.025$. This definition was similar to that used in other publications (22–24).

Table 1. Demographic and disease characteristics.

	4% SCG emulsion (n = 103)	Vehicle (n = 103)
Age (years)	5.2 (2.73)	5.5 (2.86)
Sex		
Male	46 (44.7%)	54 (52.4%)
Female	57 (55.3%)	49 (47.6%)
Ethnic origin:		
Caucasian	75 (72.8%)	75 (72.8%)
Asian	16 (15.5%)	14 (13.6%)
Black/Caribbean	10 (9.7%)	11 (10.7%)
Other	2 (1.9%)	3 (2.9%)
Height (cm)	111.0 (17.75)	112.8 (18.07)
Weight (kg)	21.13 (8.654)	22.32 (10.505)
BMI (kg/m ²)	16.56 (2.437)	16.75 (2.764)
SCORAD visit 3: (0–103)	40.8 (9.68)	40.8 (9.30)
SASSAD visit 3: (0–108)	27.3 (11.17)	28.5 (10.98)
Diary cards: (0–3)		
Overall skin condition	2.0 (0.42)	2.0 (0.49)
Itching	2.0 (0.54)	1.9 (0.47)
Sleep disturbance	1.3 (0.83)	1.3 (0.83)
Topical steroids: number of times used/day	1.20 (0.605)	1.03 (0.612)
Topical steroids: mean proportion of days used/2 weeks	0.76 (0.285)	0.70 (0.335)
Topical steroids: mean daily weight during baseline (g)	1.73 (2.236)	1.36 (1.578)
Quality of life score (CDLQI) at visit 3	10.9 (6.74)	10.2 (5.61)
Quality of life score (IDQOL) at visit 3	9.7 (5.75)	8.8 (4.57)

Figures are mean ± SD or numbers (%): (scale).

Table 2 SCORAD: Change from visit 3 (baseline) to visit 7 (end of trial) by visit—full analysis set.

Clinic visit	4% SCG emulsion Mean (SD) n = 99	Vehicle Mean (SD) n = 100	ANOVA p value (treatment)	Least square mean difference 95% CI
Visit 4	−7.0 (9.74)	−4.5 (10.10)	0.0942	−2.3 −5.02; 0.40
Visit 5	−9.1 (11.04)	−6.9 (10.18)	0.1936	−1.9 −4.79; 0.98
Visit 6	−10.4 (11.70)	−6.3 (11.07)	0.0249	−3.6 −6.68; −0.46
Visit 7	−11.2 (12.49)	−7.8 (13.55)	0.0884	−3.1 −6.60; 0.46

Table 3 SCORAD: Change from visit 3 (baseline) to visit 7 (end of trial) by visit—per protocol population.

Clinic visit	4% SCG emulsion Mean (SD) n = 64	Vehicle Mean (SD) n = 63	ANOVA p value (treatment)	Least square mean difference 95% CI
Visit 4	−7.9 (9.18)	−5.1 (10.60)	0.1106	−2.8 −6.15; 0.64
Visit 5	−10.5 (9.39)	−8.1 (9.64)	0.1831	−2.3 −5.65; 1.09
Visit 6	−12.1 (10.39)	−7.5 (10.27)	0.0303	−4.1 −7.87; −0.40
Visit 7	−14.8 (11.08)	−9.8 (13.39)	0.0436	−4.5 −8.78; −0.13

Table 4. SASSAD: Change from visit 3 (baseline) to visit 7 (end of trial) by visit—full analysis set.

Clinic visit	4% SCG emulsion Mean (SD) n = 99	Vehicle Mean (SD) n = 100	ANOVA p value (treatment)	Least square mean difference 95% CI
Visit 4	−4.4 (7.45)	−2.2 (8.96)	0.0381	−2.3 −4.53; −0.13
Visit 5	−5.5 (8.63)	−3.8 (8.18)	0.1000	−1.9 −4.09; 0.36
Visit 6	−6.3 (7.97)	−2.7 (8.71)	0.0014	−3.7 −5.99; −1.47
Visit 7	−6.4 (9.56)	−5.3 (9.83)	0.2592	−1.5 −3.98; 1.08

Table 5. Concomitant treatments used during baseline and throughout trial.

	4% Sodium cromoglicate	Vehicle
Emollients alone	10	18
Emollients + mildly potent steroids ^a	12	12
Emollients + moderately potent steroids ^a	20	22
Emollients + potent steroids ^a	57	48
Emollients + very potent steroids ^a	0	0
Total	99	100

^aN.B. Potency classification according to British National Formulary.

Table 6. Change from baseline in weight of topical steroid used (g/day).

Period	4% SCG Mean (SD)	Vehicle Mean (SD)	ANOVA p value for treatment difference	LS-mean difference 95% CI
Weeks 5–6	−0.29 (1.323) n = 76	0.09 (1.175) n = 67	0.1846	−0.24 −0.698; 0.118
Weeks 7–8	−0.29 (1.526) n = 72	0.01 (0.891) n = 68	0.6516	−0.08 −0.450; 0.283
Weeks 9–10	−0.72 (2.025) n = 66	−0.12 (0.826) n = 63	0.3366	−0.18 −0.536; 0.185
Weeks 11–12	−0.95 (1.962) n = 66	−0.03 (1.167) n = 58	0.0048	−0.53 −0.903; −0.166
Weeks 13–14	−0.88 (1.570) n = 65	−0.13 (1.077) n = 57	0.0087	−0.46 −0.807; −0.119
Weeks 15–16	−0.60 (1.297) n = 62	−0.05 (1.055) n = 54	0.0384	−0.39 −0.750; −0.021

Test treatment use

The amount of test treatment applied each day during the first and last 2 weeks of the double-blind period is given in Table 8.

Adverse events

During the double-blind period, 49 recorded adverse events were considered to be either certainly or possibly treatment related: 27 (18 subjects, 17.5%) in the 4% SCG group and 22 (19 subjects, 18.4%) in the vehicle group. The majority of treatment-related adverse events referred to discomfort at the site of application. This was reported by 30 subjects: 13 (12.6%) in the 4% SCG group and 17 (16.5%) in the vehicle group. Application-site

Table 7. Global opinions of treatment—full analysis set.

	4% SCG emulsion (n = 99)		Vehicle (n = 100)		Odds ratio (95% CI)	p value
	Very/moderately effective	Slightly effective/no effect/made condition worse	Very/moderately effective	Slightly effective/no effect/made condition worse		
Parent	56 (61.5%)	35 (38.5%)	40 (43.0%)	53 (57.0%)	1.4203 (1.0682; 1.8885)	0.015
Physician	63 (69.2%)	28 (30.8%)	47 (52.2%)	43 (47.8%)	1.3139 (1.0361; 1.6660)	0.025

Table 8. Amount of test treatment applied (g/m²).

Period	4% SCG emulsion Mean ± SD	Vehicle Mean ± SD
First 2 weeks	91.5 ± 50.37	92.0 ± 51.78
Final 2 weeks	80.8 ± 55.55	87.4 ± 53.13

Body surface area is calculated using Dubois formula.

discomfort resulted in treatment being stopped in 16 cases (4% SCG-5, vehicle-11).

Discussion

This study was an adjunctive 12-week randomised controlled trial, in which 4% SCG emulsion or vehicle was added to the existing treatment of children aged 2 to 12 years with AD. The existing treatment consisted of emollients in all subjects and emollients together with topical steroids in the majority. At randomisation, the SCORAD score, the primary outcome measure, indicated moderately severe AD. The SCORAD score was reduced in both treatment groups, the difference in the reduction being greater throughout the trial in the 4% SCG emulsion group compared to the vehicle group, achieving statistical significance after 8 weeks treatment and just failing to achieve significance at 12 weeks. As the reduction in concomitant topical steroid use was significantly greater in the 4% SCG group, this would tend to reduce the difference between the two treatments, which may account for the loss of significance at 12 weeks. In the per protocol group, the difference was significant at both 8 and 12 weeks.

The significant reduction in the SCORAD score, which had not changed during the 4-week baseline on existing treatment, combined with a significant reduction in the amount of concomitant steroids clearly demonstrates a beneficial treatment.

The differences in objective measures of response between SCG and vehicle were reflected in the global assessments by investigators and parents, both of which were significantly superior for SCG. Treatment success, defined as an investigator global assessment of very or moderately effective, was observed significantly more frequently in the SCG group.

Conclusions

It is concluded that this 4% SCG cutaneous emulsion provides an effective, clinically useful and safe treatment for atopic dermatitis in children with demonstrable steroid-sparing benefit.

Acknowledgements

The authors wish to acknowledge the contribution made by the following people to the completion of this study:
Personnel at SynteractHCR, United Kingdom, Limited and SynteractHCR Deutschland GmbH, who identified the centres and monitored and analysed the study.
Dr. N. Morar at Chelsea and Westminster Hospital NHS Trust who entered subjects.

Drs. E. E. A. Abdulhakim, H. Shaw, H. Thomas all of Synexus Dedicated Research Centres, who also entered subjects.

Declaration of interest

A. M. Edwards and M. T. Stevens are consultants to the manufacturers of the 4% SCG emulsion and vehicle used in this study.

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