Comparison of lotions, creams, gels and ointments for the treatment of childhood eczema: the BEE RCT

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Disclosure of interests of authors

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Oxford (Oxford, UK) on an educational grant funded by Pfizer Inc. (Pfizer Inc., New York, NY, USA), unrelated to the submitted work. J Athene Lane is a member of the NIHR Clinical Trials Unit Standing Advisory Committee (2021–present) and a clinical trials unit funded by NIHR. Stephanie MacNeill is currently a member of the NIHR HTA General Committee (August 2020–present). Matthew J Ridd is a member of NIHR In-Practice Fellowship Selection Committee (2020–present), and was previously a member of the NIHR Systematic Reviews Programme Advisory Group (2019–20) and the NIHR HTA General Committee (2016–19). Amanda Roberts was previously a member of the Pharmaceuticals Panel, and a member of the NIHR HTA General Committee (2017–21) and HTA Fast Track Committee (2010–12). Miriam Santer has received funding for other NIHR projects and is a panel member for NIHR PGfAR (2018–present). Hywel C Williams directed the NIHR HTA programme from 2015 to 2020, which funded this study. He had no role to play in the funding decision.

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Scientific summary

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Scientific summary

Background

Eczema (also called atopic eczema/dermatitis) is a common condition that usually first appears in early childhood. It is characterised by dry, itchy skin. Emollients are recommended for all patients, used as a 'leave-on' treatment to add and help retain moisture in the skin. For all but the mildest disease, they are used in combination with topical anti-inflammatory (topical corticosteroids or calcineurin inhibitors) to treat and prevent eczema flare-ups.

Despite the accepted importance of emollients in treating the dry skin of eczema, there is limited evidence to guide prescribers and users on what types to use. In previous research, parents/carers (hereafter, parents) of children with eczema have spoken of a 'trial and error' approach to finding an emollient that suits them and their child, with the attendant frustration, waste and costs to both users and the health service.

Objectives

We sought to:

- compare the effectiveness and acceptability of four commonly used types of emollients (lotion, cream, gel and ointment) in the treatment of childhood eczema
- explore carers' and children's experiences of study emollient use and their views about perceived effectiveness and/or acceptability of study emollients.

Methods

We recruited children with eczema via general practitioners' (GPs') surgeries based in three centres (West of England, Wessex and East Midlands). To be eligible, children had to be aged between 6 months and 12 years and to have at least a mild form of disease, and parents had to be willing to be randomly allocated to any of the types as their main emollient. Children with a known sensitivity to study emollients or their constituents were excluded. Participants were randomised to lotion, cream, gel or ointment groups in a 1 : 1 : 1 : 1 manner, stratified by centre and minimised by baseline eczema severity as determined by the Patient Orientated Eczema Measure (POEM) score [mild (3–7 points) vs. moderate/severe (≥ 8 points)] and participant age (< 2 years vs. ≥ 2 years).

Participants received their allocated type of emollient via their GP, who prescribed products on their local formulary that were study approved. All study emollients were paraffin based and none contained antimicrobials or urea. Study lotions contained glycerol [Cetraben (Thornton & Ross Ltd, Huddersfield, UK), Diprobase (Bayer UK Ltd, Reading, UK), QV (QV Skincare, Melbourne, VIC, Australia)], study creams had no humectant or lanolin [AproDerm (Fontus Health, Walsall, UK), Aquamax (Intrapharm Laboratories, Maidenhead, UK), Diprobase, Epimax (Aspire Pharma, Petersfield, UK), Zerobase (Thornton & Ross Ltd, Huddersfield, UK)], gels did not contain povidine [AproDerm (Fontus Health, Walsall, UK), Doublebase (Diomed Developments, Hitchin, UK), Isomol (Aspire Pharma, Petersfield, UK), MyriBase (Penlan Healthcare,Weybridge, UK) and Zerodouble (Thornton & Ross Ltd, Huddersfield, UK)] and study ointments had no additives (Diprobase, Emulsifying, Paraffin White soft, Paraffin Yellow soft ointment, White soft/Liquid paraffin 50/50). Participants were asked to use their study emollient as their only leave-on treatment for the first 16 weeks; thereafter, they were free to change. However, if they had problems with or disliked their study emollient, they could stop it and seek an alternative from their GP.

Participants' skin was assessed using the Eczema Area Severity Index (EASI) at baseline and at 16 weeks by a researcher masked to treatment allocation. Other data were collected by self-completed questionnaires weekly (first 16 weeks) and then 4-weekly (until 52 weeks). The primary outcome was eczema symptoms measured using the POEM over 16 weeks. We sought to recruit 520 children to detect a difference of 3.0 points in POEM scores between any two groups with 90% power and a significance level of 0.05, allowing for 20% loss to follow-up and multiple comparison testing.

We conducted semistructured interviews with parents and older children at around 4 weeks and 16 weeks after randomisation, sampling on the characteristics of the children. The interviews were conducted face to face and by telephone, informed by a topic guide that was revised during the course of the study. Interviews were audio-recorded and transcribed verbatim. Analysis was thematic and carried out alongside data collection, which stopped once saturation was reached.

Ethics approval was granted by the NHS Research Ethics Committee (South West – Central Bristol Research Ethics Committee 17/SW/0089).

Results

Between January 2018 and October 2019, 78 GP surgeries sent 9437 invitations to potentially eligible children. Expressions of interest were received from 910 parents, and 550 children attended a baseline visit, were eligible and enrolled. At baseline, the characteristics of participants were balanced except for sex, as there were more girls in the cream group (55%) than in the gel group (40%). Most children were white (86.0%), with a median age of 4 years (interquartile range 2–8 years) and moderate severity eczema (mean POEM score 9.32 points; standard deviation 5.46 points). Creams (94.5%) were most likely to have been used before, followed by ointments (66%), lotions (63.0%) and gels (25.0%).

Participants were randomised to receive lotion (n = 137), cream (n = 140), gel (n = 135) or ointment (n = 138), with prescriptions issued by their GP. The median number of days between randomisation and reported first use of emollient was 4 days (interquartile range 3–7 days), with 80% reporting first use within 7 days of randomisation. There were 29 withdrawals (24 in the first 16 weeks). A total of 95% of participants provided at least one post-baseline POEM score and, therefore, were included in the primary outcome analysis. The researcher undertaking the EASI assessment identified the correct allocation in seven participants.

There was no difference in the primary outcome (repeated-measures analysis of weekly POEM scores over the first 16 weeks) between the different groups (global p = 0.765). The adjusted differences in mean POEM scores [95% confidence interval (CI)] for pairwise comparisons were as follows: lotion versus cream 0.42 (95% CI −0.48 to 1.32; p = 0.360); lotion versus gel 0.17 (95% CI −0.75 to 1.09; p = 0.718); lotion versus ointment −0.01 (95% CI −0.93 to 0.91; p = 0.983); cream versus gel −0.25 (95% CI −1.15 to 0.65; p = 0.586); cream versus ointment −0.43 (95% CI −1.34 to 0.48; p = 0.354); and gel versus ointment −0.18 (95% CI −1.11 to 0.75; p = 0.704). Adjusting for sex imbalance at baseline and imputing missing data using multiple imputation did not meaningfully alter these results. There was no evidence of a difference in mean POEM scores between treatment groups or in any of the pairwise comparisons in first 16 weeks in 'per-protocol' analysis (p = 0.238) or over the 52 weeks (p = 0.909). There was no evidence of effect modification in prespecified subgroup analyses by parent prior emollient expectation (p = 0.935), participant age (p = 0.343), participant eczema severity (p = 0.042), or UK diagnostic criteria for atopic dermatitis (p = 0.291).

No differences between groups were seen in the following secondary outcomes at 16 weeks (or 52 weeks, if also collected): EASI scores, Atopic Dermatitis Quality of Life scores, Child Health Utility 9-Dimension scores, Dermatitis Family Impact scores and well-controlled weeks. During the first 16

weeks, median reported weekly use of the allocated emollient appeared to be higher in the lotion and cream groups (6 days per week) and lower in the gel (5 days) and ointment (3 days) groups, but this difference in usage was not statistically significant (p = 0.481). Similarly, there was no difference between groups in median reported daily use of non-allocated emollient or topical corticosteroids. Overall satisfaction was highest with lotions and gels (67.3% and 64.5% very or mostly satisfied, respectively) and dissatisfaction was highest with creams and ointments (34.2% and 40.4% dissatisfied or very dissatisfied, respectively) (p = 0.003).

Overall, 37% of participants reported at least one adverse reaction, the most common being 'application site reactions' (e.g. worsening of eczema). There was no evidence that the proportion of children reporting adverse reactions in the first 16 weeks of follow-up differed by treatment group (p = 0.794). There were no significant adverse events.

In the nested qualitative study, 44 parents were interviewed, 20 at both weeks 4 and 24 (including five repeat interviews at week 16). Children took part in 25 interviews. Participants judged the effectiveness of study emollients by comparing them with others they had used in the past (i.e. the perceived hydrating action of the emollient, skin feel after application, skin symptoms and appearance, the number of flare-ups, and the need for topical corticosteroid use). Other factors identified as affecting effectiveness were weather and the frequency and quantity of emollient application. Acceptability was usually considered alongside or as part of the effectiveness of an emollient. Characteristics of the emollients that participants considered were how it felt on the skin, ease of application and absorbency, with smell being less important. In terms of containers, participants favoured pumps and squeezer bottles for practical reasons, including older child being able to self-apply.

Many participants in the lotion and gel groups reported ease of application but felt that these types of emollients had to be used more often, and there was a perception that they 'maintained' rather than improved the skin. Although participants using study creams and study ointment were more likely to report improvements, opinions about their acceptability were more divergent. Problems were reported with all types of emollients. At 16 weeks, there was no clear pattern or differentiation between the emollient types in terms of continued use over and above the factors listed above.

Parents of children with very dry and/or rough skin tended to prefer an emollient with a thicker consistency, such as a cream or an ointment. Age was also reported to influence emollient use: application may be easier/more frequent in younger children, accompanying nappy changes, and more difficult in older children as they become more independent and attend school. Some participants thought that their child's eczema and the effectiveness of their emollient was related to their ethnicity.

Changes in behaviour and knowledge were reported as a result of taking part in the trial. For some, the regular study questionnaires had reminded them to apply their emollient regularly. Others reported persisting more with one treatment or that the emollient information sheet had improved their knowledge of eczema management.

Conclusions

No one type of emollient was found to be superior, although these findings may not apply to children from more ethnically diverse backgrounds. Parents and children should be made aware that application site reactions are common; persistence may be required to find an emollient that works for them; and preferences may change with time, season and body site. We have also demonstrated the need for choice and education around the use of emollients for the treatment of eczema in children. Without this, emollients may be applied incorrectly or not as frequently as prescribed. Most children with eczema will need, in addition to their emollient, a topical anti-inflammatory treatment (usually corticosteroids) appropriate to the site and severity of their eczema to get, and keep, control of their condition.

Guidelines should advocate for, and formularies support, a range of emollients, with lotions, creams, gels and ointments all available. Prescribers and pharmacists have an important role in ensuring that families are aware of the different emollients available, to support them in selecting a type most likely to suit them and to advise on optimal use. Verbal advice could be accompanied by written or online information (including videos) on the role of emollients and how to use them, perhaps accompanied by a planned review at the end of an agreed trial period.

Future research could evaluate a decision aid to support parents and clinicians in deciding which type of emollient to try first and the clinical effectiveness and cost-effectiveness of providing 'tester pots' of each type of emollient to try before selecting their preferred emollient. Further trials may be appropriate to compare emollients in more ethnically diverse populations and of different types not evaluated in this study, for example ointments with emulsifiers and humectant-containing, plant-based and 'novel' emollients, including those designed to alter the skin microbiome. Research in this field would benefit from an internationally agreed system of classifying different emollients and a common approach to measuring and reporting treatment use. Finally, further research is needed to determine how emollients best fit into an overall package of eczema care, which includes frequency of use, bathing, use of other topical treatments and avoidance of triggers.

Trial registration

This trial is registered as ISRCTN84540529 and EudraCT 2017-000688-34.

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This report

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