

Original Investigation

Clobetasol Propionate, 0.05%, vs Hydrocortisone, 1%, for Alopecia Areata in Children

A Randomized Clinical Trial

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IMPORTANCE Alopecia areata is an idiopathic cause of hair loss with limited therapeutic repertoire.

OBJECTIVE To compare the efficacy and safety of a high- vs low-potency topical corticosteroid in pediatric patients.

DESIGN, SETTING, AND PARTICIPANTS This single-center, randomized, blind, 2-arm, parallel-group, superiority trial was carried out over a 24-week period at a tertiary referral academic dermatology clinic at The Hospital for Sick Children in Toronto, Ontario, Canada. Forty-two children attending the outpatients clinic, 2 to 16 years of age with alopecia areata affecting at least 10% of scalp surface area, were eligible; 1 declined to participate. There were no withdrawals from the study.

INTERVENTIONS FOR CLINICAL TRIALS Patients were randomly assigned to receive clobetasol propionate, 0.05% cream, or hydrocortisone, 1%, cream. Patients applied a thin layer of the assigned cream twice daily to the areas of hair loss for 2 cycles of 6 weeks on, 6 weeks off, for a total of 24 weeks.

MAIN OUTCOMES AND MEASURES The primary outcome was the change in scalp surface area with hair loss over 24 weeks following enrollment.

RESULTS All participants were assessed at 6, 12, 18, and 24 weeks (except 1 participant who missed the 6-week visit). After adjusting for baseline hair loss, the clobetasol group had a statistically significant ($P < .001$) greater decrease in the surface area with hair loss, compared with the hydrocortisone group at all time points except at 6 weeks. One patient with extensive alopecia areata experienced skin atrophy that resolved spontaneously in 6 weeks. There was no difference observed in the number of patients with abnormal urinary cortisol at the beginning and the end of the study.

CONCLUSIONS AND RELEVANCE Topical clobetasol propionate, 0.05%, cream is efficacious and safe as a first-line agent for limited patchy childhood alopecia areata.

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Alopecia areata is a nonscarring autoimmune idiopathic cause of hair loss with a prevalence of 0.1% and a lifetime risk of 1.7%.¹ Pediatric cases account for 20%,^{2,3} and the condition can be associated with psychological distress in affected children and their families. There is a limited therapeutic repertoire for alopecia areata. Topical steroids are the most common therapy used. However, a recent Cochrane Systematic Review⁴ concluded that there is scant evidence for the long-term therapeutic benefit of steroids in alopecia areata, and that there is a “desperate need” for well-constructed therapeutic trials. To our knowledge, no prospective studies in children have examined any of the existing topical modalities for alopecia areata. The primary objective of our study was to determine the efficacy and safety of a class 1 topical steroid (clobetasol propionate, 0.05%) compared with a class 7 topical steroid (hydrocortisone, 1%) in the treatment of pediatric alopecia areata.

Methods

This was a single-center, randomized, blind, 2-arm, parallel-group, superiority trial. We consecutively enrolled patients attending a tertiary referral academic dermatology clinic at The Hospital for Sick Children in Toronto, Ontario, Canada, from August 2002 to August 2003. The study received ethical approval from the hospital research ethics board. Children 2 to 16 years of age with a clinical confirmation of alopecia areata and at least 10% of their scalp surface area affected, whose parents provided written informed consent, were included. Exclusion criteria included any skin or medical condition requiring oral corticosteroids, immunosuppressants, or light therapy within 4 weeks prior to the study; use of inhaled or intranasal steroids during the 14 days prior to enrollment; and/or any topical medications during the 7 days prior to enrollment.

Patients were randomly assigned by the hospital research pharmacist to either clobetasol propionate, 0.05%, cream, or hydrocortisone, 1%, cream using a computer-generated random number system to maintain allocation concealment (hereinafter, clobetasol group and hydrocortisone group, respectively). Block randomization with a block size of 4 and a balanced allocation was used. The investigators, attending physicians, parents, and patients were blinded to the group allocation. Patients were instructed to apply a thin layer of the assigned cream twice daily to the areas of hair loss for 2 cycles of 6 weeks on, 6 weeks off for a total of 24 weeks (cycling is a common practice used to decrease systemic absorption). Patients were supplied weekly with 50-g identical jars containing creams similar in texture, color, and smell to maintain blinding.

The primary outcome of interest was change in scalp surface area with hair loss over time. Hair loss at baseline was measured by tracing the area of alopecia onto acetate sheets and then onto graph paper and calculating the affected surface area (in centimeters squared). Surface area with hair loss was measured at 6, 12, 18, and 24 weeks following enrollment. All measurements were performed by the same assessor (P.L.), a trained dermatologist, who was also blinded.

Secondary outcomes included (1) the percentage of change in scalp surface area with hair loss between baseline and 24 weeks; (2) at least 50% reduction in scalp surface area with hair loss from baseline to 24 weeks; and (3) the frequency of adverse events such as skin atrophy, striae, or local symptoms. In addition, any evidence of hypercortisolemia or adrenal suppression was assessed by performing 24-hour urinary collection and serum cortisol levels.

Sample Size Calculation

To detect an absolute difference of 10% in the scalp surface area with hair loss between the 2 groups—at a significance level of 5% and a power of 80%, using a repeated measures analysis—a sample size of 20 participants per group was required.

Statistical Analysis

An intention to treat analysis was performed. The primary analysis used repeated measures analysis of covariance, controlling for baseline scalp surface area with hair loss. Scalp area affected was log transformed for the analysis, and standard deviations were calculated using the δ method.⁵ The percentage of change in scalp surface area with hair loss from baseline to 24 weeks was compared between treatment groups using the Wilcoxon rank sum test. The proportion of patients with at least 50% reduction in scalp surface area with hair loss from baseline to 24 weeks was compared between treatment groups using the χ^2 test.

The study followed CONSORT recommendations for reporting of randomized clinical trials.⁶

Results

Forty-two children were assessed for eligibility, and 41 (23 of whom were female) were randomly assigned to the treatment groups. The age of the patients ranged from 2 to 15 years (mean, 7.3 years). Atopic dermatitis was the most common medical problem and was seen in 65% (15 of 23 patients). Twenty-one patients had a history of alopecia areata. Eight patients had never received treatment prior to starting the trial. The remainder had used a variety of medications, including topical, oral, and intramuscular corticosteroids; tretinoin; anthralin; terbinafine hydrochloride; topical tacrolimus; diphenhydramine; phototherapy; coal tar; minoxidil; and Chinese herbal medicine. Multiple treatments were administered to 17 of 33 patients.

Two patients had a history of other autoimmune conditions (hypothyroidism), 1 in each group. Five patients had a family history of alopecia areata, 10 had family members with thyroid disease, 7 had a family history of diabetes mellitus, and 4 had family members with autoimmune disease (2 had vitiligo; 1, rheumatoid arthritis; and 1, immune thrombocytopenia).

Twenty children were assigned to the clobetasol treatment group and 21 to the hydrocortisone group. All patients were assessed at 6, 12, 18, and 24 weeks (except 1 patient who missed the 6-week visit).

Baseline data were similar for the 2 groups (Table 1), other than baseline surface area with hair loss, which was higher in the clobetasol group compared with the hydrocortisone group (median loss, 72.2 cm² vs 49.2 cm², respectively).

The clobetasol group had a greater decrease in the scalp surface area with hair loss when compared with the hydrocortisone group ($P < .001$) (Figure). After adjusting for baseline hair loss and treatment duration (Table 2), the clobetasol group had a statistically significant greater decrease in the surface area with hair loss compared with the hydrocortisone group at all time points (12, 18, and 24 weeks), other than at 6 weeks.

The percentage of reduction in scalp surface area with hair loss at 24 weeks compared with baseline was greater in the clobetasol group (96.5%; IQR, 64%-100%) compared with the hydrocortisone group (4.6%; IQR, -444.3% to 80.8%) ($P = .002$) (Table 3). Seventeen of 20 children in the clobetasol group (85%) vs 7 of 21 children in the hydrocortisone group (33.3%) had a at least a 50% reduction in surface area with hair loss at 24 weeks ($P < .001$).

No patients complained of a stinging or burning sensation while using the cream. One patient with extensive alopecia areata treated with clobetasol experienced atrophy of the scalp skin; however, this completely resolved after the 6-week period without any treatment.

Abnormally low urinary cortisol levels were noted at baseline in 2 of 17 patients in the hydrocortisone group vs 7 of 16 patients in the clobetasol group ($P = .04$), which was likely reflective of prior steroid treatment. There was no difference in the numbers of patients with an abnormal cortisol level at the end of the study (6 of 17 vs 5 of 16; $P = .81$). Moreover, 2 of 2 patients in the hydrocortisone group and 6 of 7 of the patients in the clobetasol group who had abnormal baseline cortisol levels had normal levels by the end of the study.

Table 1. Baseline Characteristics for Clobetasol Propionate, 0.05%, vs Hydrocortisone, 1%

Variable	Group	
	Clobetasol Propionate, 0.05% (n = 20)	Hydrocortisone, 1% (n = 21)
Female, No. (%)	12 (57)	11 (55)
Age, mean (SD), y	7.8 (3.7)	7.0 (3.6)
Baseline surface area with hair loss, median (IQR), cm ²	72.2 (31.2-126.6)	49.2 (27.3-75.4)
Previous steroid treatment for alopecia areata, No. (%)	11 (55)	10 (48)

Abbreviation: IQR, interquartile range.

Table 2. Surface Area With Hair Loss Over Time in the Treatment Groups^a

Weeks	Group		P Value
	Clobetasol Propionate, 0.05% (n = 20)	Hydrocortisone, 1% (n = 21)	
6	18.7 (8.3-40.6)	45.3 (21.5-94.3)	.11
12	6.3 (2.5-14.3)	42.2 (20.0-88.0)	.001
18	5.5 (2.1-12.6)	51.6 (24.5-107.3)	<.001
24	3.1 (0.9-7.6)	55.0 (26.2-114.3)	<.001

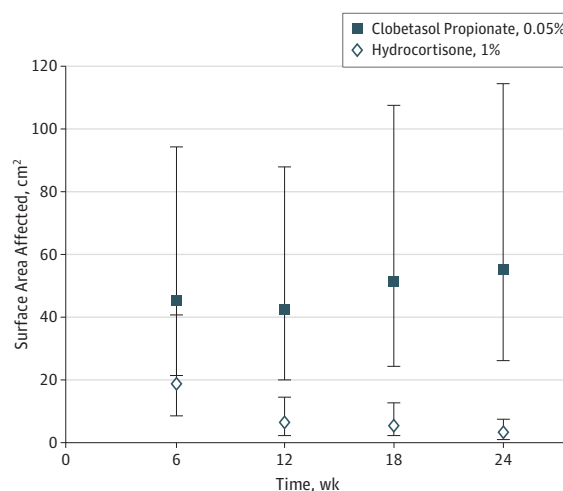
^a Data are given as median (95% CI) centimeters squared.

Discussion

This randomized clinical trial involving children and adolescents with alopecia areata demonstrated that treatment with topical clobetasol, 0.05%, led to clinically significant hair regrowth at 24 weeks, compared with treatment with topical hydrocortisone, 1%.

Alopecia areata can be associated with significant psychological and social distress, with most patients reporting quality-of-life issues, based on a Dermatology Life Quality Index.⁷ Because of this, many patients and their families seek treatment. A 2008 Cochrane Systematic Review⁴ reported on interventions for alopecia areata. The review summarized data from 17 randomized clinical trials involving 540 participants, with trial sample sizes ranging from 6 to 85. Therapeutic options reviewed included topical minoxidil, oral steroids, phototherapy, and topical cyclosporine. None of the studies were restricted to children alone, and only 3 included children. The authors concluded that there was a lack of evidence for any of the topical, intralesional, or systemic interventions in alopecia areata. Furthermore, they strongly recommended that future trials be adequately powered, conducted in a homoge-

Figure. Median Scalp Area Affected in the Clobetasol Propionate, 0.05%, and Hydrocortisone, 1%, Groups Over Time



Baseline surface area with hair loss: clobetasol propionate, 0.05%, group, 72.2 cm²; hydrocortisone, 1%, group, 49.2 cm². Error bars indicate medians with 95% CIs.

Table 3. Comparison of Secondary Outcomes

Variable	Group		P Value
	Clobetasol Propionate, 0.05% (n = 20)	Hydrocortisone, 1% (n = 21)	
Percentage of change in scalp surface area with hair loss from baseline to 24 weeks, median (IQR)	96.5 (63.7 to 100)	4.7 (-444.3 to 80.8)	.002
Patients with $\geq 50\%$ reduction in scalp surface area affected from baseline to 24 weeks, No. (%)	17 (85)	7 (33)	<.001

Abbreviation: IQR, interquartile range.

neous population, include a placebo or another comparison arm, and use clinically measurable outcomes.

A recent literature review also emphasized the limited therapeutic options and lack of evidence for the treatment of alopecia areata.⁸ In clinical practice, the first-line therapy in childhood alopecia areata is topical corticosteroids, particularly high-potency steroids. Recently, systemic therapies with corticosteroids,⁷ methotrexate,⁹ or azathioprine,¹⁰ or topical diphencyprone¹¹ have been reported as potential options for children with treatment-resistant alopecia areata. However, these studies were uncontrolled and retrospective or of short duration and limited by small sample sizes. To our knowledge, this study is the first randomized clinical trial in the pediatric population that provides evidence for the efficacy and safety of topical high-potency corticosteroids in children with alopecia areata.

Our results may be generalizable only to children with patchy hair loss (median surface area, 72 cm²). Diffuse alope-

cia areata makes topical applications less feasible and may increase the risk of adverse events. Furthermore, the effect of these therapies is sometimes temporary, and long-term outcomes after treatment discontinuation cannot be implied from this study.

While there was no evidence of systemic absorption of corticosteroids, abnormal cortisol levels at baseline suggested the possibility that long-term therapy may be associated with adverse events. In our study, we used a 6-week cycle of therapy to prevent adrenal suppression. Whether this practice is necessary or effective needs further study.

In conclusion, despite these limitations, our study provides evidence that topical high-potency steroids can be effective and safe as first-line agents for limited patchy childhood alopecia areata, before other, more invasive, therapies are considered. Further studies, exploring optimal duration and regimen of treatment with high-potency steroids, and comparative studies with contact immunotherapy should be undertaken.

ARTICLE INFORMATION

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Study concept and design: Lenane, MacArthur, Parkin, Krafchik.

Acquisition of data: Lenane, MacArthur.

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