Dermatology

Brief Report

Dermatology 2023;239:670–674
DOI: 10.1159/000530758

Received: January 18, 2023
Accepted: April 11, 2023
Published online: April 20, 2023

Clindamycin-Benzoyl Peroxide Gel Compared with Clindamycin Lotion for Hidradenitis Suppurativa: A Randomized Controlled Assessor-Blinded Intra-Patient Pilot Study

Pim Aarts Joanne L. Reeves Christine B. Ardon Hessel H. van der Zee
Errol P. Prens

Department of Dermatology, Erasmus University Medical Center, Rotterdam, The Netherlands

Keywords
Topical clindamycin · Hidradenitis suppurativa · Antibiotic resistance · Topical formulation · Clindamycin-benzoyl peroxide gel

Abstract
Background: Antibiotic resistance is a major concern, especially in hidradenitis suppurativa (HS). However, antibiotics form a cornerstone in its treatment. Topical clindamycin is known to cause bacterial resistance but is still advised as monotherapy for the treatment of mild to moderate HS. ***Methods:*** This is a randomized, controlled, assessor-blinded, intra-patient pilot trial to compare the clinical efficacy of clindamycin-benzoyl peroxide gel with clindamycin lotion in patients with mild to moderate HS. Two contralateral body sites were randomized for treatment in each patient. The primary outcome was the difference in the International Hidradenitis Suppurativa Severity Score (IHS4) between the two groups after 12 weeks. Secondary objectives were feasibility of the intra-patient design, efficacy within treatment groups, effect on HS pain, HS itch, patient satisfaction, antibiotic resistance, and the prolonged efficacy after 16 weeks. ***Results:*** Ten patients were included, resulting in two groups of 10 treated body sites. No significant differences were found between the two groups for all measurements after 12 or 16 weeks, while both therapies led to an improvement in the IHS4, pain, and itch scores. A significant decrease was observed in the IHS4 for both the clindamycin lotion (−1.5; $p < 0.05$) and the clindamycin-benzoyl peroxide gel (−2; $p < 0.01$) after 16 weeks, and the pain scores were reduced from 7 to 2.5, $p < 0.01$ and 6.5 to 3, $p = 0.03$, respectively. Using the IHS4-55, we identified 50% of patients as responders in both groups after 12 weeks. The intra-patient design, however, unexpectedly appeared to hinder the inclusion of patients. ***Conclusion:*** Clindamycin-benzoyl peroxide gel showed favorable clinical efficacy results, similar to clindamycin lotion, suggesting that it could replace clindamycin lotion in the treatment of mild to moderate HS and to prevent antibiotic resistance. A larger controlled trial is needed to validate these results.

Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by recurrent painful inflammatory nodules that can progress to abscesses, tunnels, and scars [1]. Although HS is not primarily an

karger@karger.com
www.karger.com/drm

Correspondence to:
Pim Aarts, p.aarts@erasmusmc.nl

infectious disease, antibiotics are a mainstay in its treatment.

Treatment guidelines recommend topical clindamycin as monotherapy for the treatment of mild to moderate HS [2]. These recommendations are based on two clinical trials which showed favorable results for topical clindamycin compared with placebo and similar results when compared with oral tetracycline [3, 4]. Furthermore, a Hidradenitis Suppurativa Clinical Response (HiSCR) of 52% was shown after 12 weeks of treatment with topical clindamycin by Molinelli et al. [5] in a retrospective study of 72 HS patients.

However, the emergence of bacterial resistance in HS is a serious concern, and high levels of resistance for rifampicin, clindamycin, and tetracyclines have already been demonstrated [6, 7]. This problem urges for a restraint on the long-term use of antibiotics and a need for preparations that are less susceptible to the induction of bacterial resistance. The current treatment guidelines for acne vulgaris already discourage the use of clindamycin as monotherapy due to the risk of bacterial resistance and instead recommend formulations that combine topical antibiotics with other active ingredients, such as benzoyl peroxide and retinoids [8]. It seems logical that topical formulations can also be used in HS; nonetheless, scientific evidence is scarce. Therefore, we sought to explore the feasibility of a randomized, controlled, assessor-blinded, intra-patient pilot trial to investigate the efficacy of clindamycin-benzoyl peroxide gel compared with clindamycin lotion monotherapy for the treatment of mild to moderate HS.

Methods

Study Design

This randomized, controlled, assessor-blinded, intra-patient pilot trial was conducted at the Department of Dermatology of the Erasmus University Medical Center, Rotterdam, The Netherlands, from November 2019 to March 2022. The aim of this trial was to compare the efficacy of clindamycin-benzoyl peroxide gel with clindamycin lotion and to evaluate the feasibility of an intra-patient study design. Contralateral body sites with comparable disease severity were randomized for treatment in blocks of two by an independent researcher in either clindamycin lotion 1% twice daily for 12 weeks or the formulation gel of clindamycin 1% with benzoyl peroxide 5% in a left-right fashion (axillary, inguinal, or gluteal) with a follow-up of 4 weeks to assess sustained efficacy. Visits were conducted by an unblinded physician assistant, and lesion count was performed by an HS investigator, blinded to treatment. Patients were asked to wear white clothes to all visits to prevent de-blinding by possible textile bleaching stains from the benzoyl peroxide. Furthermore, at each visit, the patients were asked for therapy adherence, and the remaining volume and weight of returned flasks were measured at the 12-week visit.

Participants

Adult patients with mild to moderate HS, according to the Hidradenitis Suppurativa Physician's Global Assessment scale (HS-PGA) [9], were eligible for inclusion. Other inclusion criteria were as follows: two inflammatory lesions in both, contralateral, body sites; a diagnosis of HS for more than 6 months; being able and willing to provide written consent. Exclusion criteria were as follows: a contraindication for clindamycin or benzoyl peroxide, superinfection of HS lesions, other skin condition, presence of uncontrolled disease, pregnant or lactating women, the use of systemic antibiotics 14 days prior to inclusion, and topical antibiotics or resorcinol in the eligible body sites 14 days prior to inclusion.

Assessments

The primary outcome was the difference in International Hidradenitis Suppurativa Severity Score (IHS4) [10] between the two groups after 12 weeks. Secondary objectives were difference between the two groups in IHS4-55 [11], pain scores (NRS-pain), itch scores (NRS-itch), and satisfaction scores after 12 and 16 weeks. Additionally, within-group differences were tested for IHS4, pain scores, and itch scores between baseline and 12 and 16 weeks. Furthermore, lesional swaps were taken at baseline and after 12 weeks to assess bacterial resistance for clindamycin. Safety and tolerability were checked throughout the whole study.

Statistical Analysis

Baseline characteristics are presented as median (IQR) or *n* (%). All continuous data were analyzed using the Wilcoxon matched-pair signed-rank test. For categorical variables, differences between groups were assessed using a χ^2 test or Fisher's exact test. All comparisons were two sided, and p values ≤ 0.05 were considered statistically significant. Statistical analyses were performed in SPSS Statistics 28.0 (IBM Corporation, Armonk, NY, USA).

Ethical Approval

The protocol was reviewed and approved by the Local Medical Ethical Review Board (approval number: MEC-2018-1930), and the study was conducted in accordance with the provisions of the Declaration of Helsinki.

Results

Ten patients were included with a total of twenty body sites. Most patients (80%) were female, median age was 28 [IQR: 22.5–36.3], median BMI was 32.4 [IQR: 27.1–35.6], and 4 patients (40%) were currently smoking. The axillary (40%) and inguinal (40%) body sites were most often treated, followed by the gluteal region (20%). Baseline severity, measured in Hurley staging, resulted in 90% mild patients and 10% moderate patients. However, when using the refined Hurley staging [12], 30% were

Table 1. Patient characteristics (patients, n = 10)

Patient characteristics		
Age, years, median [IQR]	28	[22.5–36.3]
Sex,* n (%)	8	(80)
BMI, median [IQR]	32.4	[27.1–35.6]
Disease duration, years, median [IQR]	10.5	[5–16.8]
Current smoker, n (%)	4	(40)
Body site, n (%)		
Axillary	4	(40)
Inguinal	4	(40)
Gluteal	2	(20)
Hurley stage, n (%)		
Hurley stage I	9	(90)
Hurley stage II	1	(10)
Refined Hurley stage, n (%)		
Mild (1A, 2A)	3	(30)
Moderate (1B, 2B)	6	(60)
Severe (1C, 2C, 3)	1	(10)

IQR, interquartile range; BMI, body mass index. *Female.

considered mild (1A), 60% moderate (1B, 2B), and 1 patient was severe (1C) (Table 1).

The IHS4 at baseline was 2 [IQR: 1.8–2] for clindamycin lotion and 2 [IQR: 2–3] for clindamycin-benzoyl peroxide gel. Both therapies lead to an improvement in the IHS4, pain scores, and itch scores, with significant improvements for the IHS4 for both the clindamycin lotion and clindamycin-benzoyl peroxide gel after 16 weeks of treatment, with a median decrease in IHS4 of −1.5 [IQR: −2 to −1], $p < 0.05$ and −2 [IQR: −2 to −1], $p < 0.01$, respectively. Furthermore, pain scores were significantly reduced in both groups after 12 weeks, as median pain scores reduced from 7 [IQR: 3.5–7.3] to 2.5 [IQR: 0.8–5.3], $p < 0.01$ and from 6.5 [IQR: 4.8–8] to 3 [IQR: 0.8–6.5], $p < 0.05$, for clindamycin lotion and clindamycin-benzoyl peroxide gel, respectively. Although the itch score showed a decline in both groups, no significant differences were found. The dichotomous IHS4 (IHS4-55) showed the same results for both groups, with 50% responders after 12 weeks and 60% responders after 16 weeks. Between the two groups, no statistically significant differences were found. Furthermore, no differences were found for all outcome measures between the two groups.

The majority of patients were satisfied with both therapies (Table 2) and they were well tolerated with only 1 patient who reported mild itching from the treatment in both body sites. A small increase in clindamycin-resistant strains was observed for clindamycin lotion, whereas the clindamycin-resistant strains with clindamycin-benzoyl peroxide gel remained stable (Table 2).

Discussion

This randomized, controlled, assessor-blinded, intra-patient pilot trial showed similar clinical results for the topical application of clindamycin lotion and clindamycin-benzoyl peroxide gel for patients with mild to moderate HS. Our results, which show a 50% efficacy in IHS4-55 for both groups after 12 weeks, are in line with previous clinical studies investigating the efficacy of topical clindamycin monotherapy in mild to moderate HS [3–5]. The similar results that were found for clindamycin-benzoyl peroxide gel suggest that this formulation is equivalent to topical clindamycin monotherapy. A shift from clindamycin monotherapy to a combination formulation in mild to moderate patients could contribute to controlling the emergence of bacterial resistance in HS, as is also advised for the treatment of acne vulgaris [8]. This is supported by the increase in clindamycin-resistant strains in the clindamycin monotherapy group compared with a minor decrease in the combination group. However, due to the small sample size, which is a clear limitation of this study, results on efficacy and bacterial resistance should be interpreted with caution and need to be validated in a larger clinical trial.

Furthermore, the feasibility of the study design caused some complications. Although the intra-patient study design reduced the required sample size and could prevent interpatient bias, it complicated patient inclusion as patients rarely presented with similar mild to moderate disease severity in both contralateral body sites. In addition, a minimum required number of four inflammatory nodules in only the two body sites formed an obstacle for the inclusion since the presence of additional inflammatory lesions in other body parts increased overall severity, causing the patient to be no longer eligible for topical therapy alone. Therefore, we would advise against the intra-patient design or to decide for a severity score of the target area.

In this study, a topical formulation was used with clindamycin and benzoyl peroxide. However, it is also possible to combine clindamycin with other compounds, such as retinoids, especially in patients with an acneiform HS phenotype [13]. We would like to encourage the initiation of clinical studies with other topical formulations to expand our topical armamentarium and to reduce antibiotic resistance.

Table 2. Clinical outcomes

	Clindamycin monotherapy (n = 10)			Clindamycin-benzoyl peroxide gel (n = 10)		
	baseline	12 weeks	16 weeks	baseline	12 weeks	16 weeks
IHS4[a], median [IQR]	2 [1.8–2]	0.5 [0–1.3]	0 [0–1]*	2 [2–3]	1 [0–2.5]	1 [0–1]**
IHS4-55, n (%)	–	5 (50)	6 (60)	–	5 (50)	6 (60)
Pain, median [IQR]	7 [3.5–7.3]	2.5 [0.8–5.3]**	3 [1–4]*	6.5 [4.8–8]	3 [0.8–6.5]*	4.5 [1.8–6.3]
Itch, median [IQR]	6 [3.8–6.3]	3 [1.5–5.3]	3.5 [0.8–6]	5 [2–7]	3.5 [2.3–5.3]	4.5 [1.5–6.3]
Satisfied, n (%)	–	8 (80)	8 (80)	–	7 (70)	6 (60)
Resistant strains[b], n	7	11	–	14	13	–

Between the two groups, no significant differences were found. All data was analyzed using the Wilcoxon matched-pair signed-rank test. IHS4, the International Hidradenitis Suppurativa Severity Score System; IQR, interquartile range. *Significance at 12 weeks and 16 week compared with baseline: $p < 0.05$. **Significance at 12 weeks and 16 week compared with baseline: $p < 0.01$. [a]IHS4 only includes lesions in the treated body site. [b]Clindamycin-resistant strains.

Conclusion

This pilot study showed favorable and similar clinical efficacy results for topical clindamycin-benzoyl peroxide gel and clindamycin lotion. However, we were confronted with the limitations of an intra-patient design for the mild to moderate HS patient population. Larger randomized controlled trials are needed to validate the efficacy of topical combination therapies and to assess their influence on the diversity and resistance patterns in the skin microbiome more extensively.

Key Message

There is less antibiotic resistance and good clinical efficacy with clindamycin-benzoyl peroxide gel in HS.

Statement of Ethics

This study protocol was reviewed and approved by the Local IRB of the Erasmus University Medical Center, approval MEC-2018-1930. This study was conducted in accordance with the provisions of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Conflict of Interest Statement

The authors have no relevant conflicts of interest to declare.

Funding Sources

No funding was received for this clinical trial.

Author Contributions

Conceptualization and writing – review and editing: all authors; data curation: Joanne L. Reeves; formal analysis and writing – original draft: Pim Aarts; investigation: Pim Aarts, Joanne L. Reeves, and Christine B. Ardon; methodology: Christine B. Ardon; and supervision: Errol P. Prens and Hessel H. van der Zee.

Data Availability Statement

Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

References

1 Sabat R, Jemec GBE, Matusiak Ł, Kimball AB, Prens E, Wolk K. Hidradenitis suppurativa. Nat Rev Dis Primers. 2020 Mar 12;6(1):18.
2 Zouboulis CC, Desai N, Emtestam L, Hunger RE, Ioannides D, Juhasz I, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. J Eur Acad Dermatol Venereol. 2015 Apr;29(4):619–44.
3 Jemec GB, Wendelboe P. Topical clindamycin versus systemic tetracycline in the treatment of hidradenitis suppurativa. J Am Acad Dermatol. 1998 Dec;39(6):971–4.
4 Clemmensen OJ. Topical treatment of hidradenitis suppurativa with clindamycin. Int J Dermatol. 1983 Jun;22(5):325–8.
5 Molinelli E, Brisigotti V, Simonetti O, Sapigni C, D'Agostino GM, Rizzetto G, et al. Efficacy and safety of topical resorcinol 15% versus topical clindamycin 1% in the management of mild-to-moderate hidradenitis suppurativa: a retrospective study. Dermatol Ther. 2022 Jun;35(6):e15439.

6 Bettoli V, Manfredini M, Massoli L, Carillo C, Barozzi A, Amendolagine G, et al. Rates of antibiotic resistance/sensitivity in bacterial cultures of hidradenitis suppurativa patients. J Eur Acad Dermatol Venereol. 2019 May;33(5):930–6.
7 Fischer AH, Haskin A, Okoye GA. Patterns of antimicrobial resistance in lesions of hidradenitis suppurativa. J Am Acad Dermatol. 2017 Feb;76(2):309–13.e2.
8 Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016 May;74(5):945–73.e33.
9 Zouboulis CC, Del Marmol V, Mrowietz U, Prens EP, Tzellos T, Jemec GB. Hidradenitis suppurativa/acne inversa: criteria for diagnosis, severity assessment, classification and disease evaluation. Dermatology. 2015;231(2):184–90.
10 Zouboulis CC, Tzellos T, Kyrgidis A, Jemec GBE, Bechara FG, Giamarellos-Bourboulis EJ, et al. Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS4), a novel dynamic scoring system to assess HS severity. Br J Dermatol. 2017 Nov;177(5):1401–9.
11 Tzellos T, van Straalen KR, Kyrgidis A, Alavi A, Goldfarb N, Gulliver W, et al. Development and validation of IHS4-55, an IHS4 dichotomous outcome to assess treatment effect for hidradenitis suppurativa. J Eur Acad Dermatol Venereol. 2023;37:395–401.
12 Horváth B, Janse IC, Blok JL, Driessen RJ, Boer J, Mekkes JR, et al. Hurley staging refined: a proposal by the Dutch hidradenitis suppurativa expert group. Acta Derm Venereol. 2017 Mar 10;97(3):412–3.
13 Dudink K, Aarts P, Ardon CB, Vossen A, Koster SBL, Van den Bosch JF, et al. Prevalence and clinical characteristics of hidradenitis suppurativa phenotypes in a large Dutch cohort. Dermatology. 2021 Oct 14;238:600–2.