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Cutibacterium acnes persists despite topical clindamycin and benzoyl peroxide

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Background: *Cutibacterium* (formerly *Propionibacterium*) *acnes* persists in the dermis despite standard skin antiseptic agents, prompting some surgeons to use topical antimicrobials such as benzoyl peroxide and clindamycin prior to shoulder arthroplasty surgery. However, the efficacy of these topical agents has not been established.

Methods: The upper backs of 12 volunteers were randomized into 4 treatment quadrants: topical benzoyl peroxide, topical clindamycin, combination topical benzoyl peroxide and clindamycin, and a negative control. The corresponding topical agents were applied to each site twice daily for 3 days. A 3-mm dermal punch biopsy specimen was obtained from each site and cultured for 14 days to assess for *C acnes* growth. Positive cultures were assessed for the hemolytic phenotype. The McNemar test was used to compare the proportion of positive cultures in each group.

Results: *C acnes* grew in 4 of 12 control sites (33.3%), 1 of 12 benzoyl peroxide sites (8.3%), 2 of 12 clindamycin sites (16.7%), and 2 of 12 combination benzoyl peroxide–clindamycin sites (16.7%). The *C acnes* hemolytic phenotype was present in 2 of 12 control specimens (16.7%) compared with 0 (0.0%) in the benzoyl peroxide group, 2 of 12 (16.7%) in the clindamycin group, and 2 of 12 (16.7%) in the combination benzoyl peroxide–clindamycin group. There were no statistically significant differences between treatment arms.

Conclusion: The topical application of benzoyl peroxide and clindamycin did not eradicate *C acnes* in all subjects. The clinical implications of these findings are yet to be determined.

Level of evidence: Level II; Prospective Cohort Design; Treatment Study

Keywords: Shoulder; *C acnes*; *P acnes*; topical antibiotics; skin antisepsis

Cutibacterium (formerly *Propionibacterium*) *acnes* is a gram-positive anaerobe responsible for the vast majority of infections following shoulder surgery[5,21] and is the most common organism responsible for delayed implant infections after shoulder arthroplasty.[16,19,21] *C acnes* colonization of the axilla, shoulder, upper back, and face is

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greater than that of other regions of the body because of the high density of pilosebaceous glands where this organism resides.[23] As shoulder arthroplasty continues to gain popularity in the United States,[3,18,28] preoperative eradication of *C acnes* continues to be an important issue to combat postoperative periprosthetic infections of the shoulder.

Intravenous antimicrobial prophylaxis with cefazolin[20] or combination cefazolin and doxycycline[23] may be ineffective at eradicating deep tissue inoculation with *C acnes*.[15] This realization has prompted some shoulder surgeons to use topical antimicrobial agents. Recent studies have found that topical benzoyl peroxide and clindamycin may decrease *C acnes* bacterial loads on the skin prior to shoulder surgery.[4,10,25] However, only 1 study has assessed the efficacy of topical benzoyl peroxide at eradicating *C acnes* in the dermis,[10] the layer of the skin where previous studies have found standard preoperative antiseptic agents to provide inadequate eradication of *C acnes*.[6,11] No study to our knowledge has examined the efficacy of combination benzoyl peroxide and clindamycin in eradicating *C acnes* from the dermal layer. As such, these topical antimicrobial agents have not been correlated with decreased infection rates following shoulder surgery. The efficacy of these topical antimicrobials at eradicating *C acnes* in the dermis has not been well established.

The purpose of this study was to compare the efficacy of topical benzoyl peroxide monotherapy, topical clindamycin monotherapy, and combination topical benzoyl peroxide and clindamycin at eradicating *C acnes* in the dermal layer of the skin. We hypothesized that combination therapy would be more efficacious than either monotherapy and would demonstrate greater eradication of *C acnes* than other previously investigated sterilization techniques.

Materials and methods

Twelve healthy volunteers older than 18 years were consented to participate. Individuals with active acne, with an ongoing infection, or who received a course of antibiotics within 1 month of study enrollment were excluded. The upper back of each subject was randomized into 4 treatment quadrants: (1) 5% topical benzoyl peroxide (BP), (2) 1% topical clindamycin, (3) 5% topical benzoyl peroxide and 1% clindamycin, and (4) a negative control. These agents were selected as the dermatologic literature supports the use of benzoyl peroxide and clindamycin gel as antimicrobial agents to treat *C acnes*[12,26] and several clinical studies have used these agents.[4,10,25,26] Furthermore, combination therapy using antimicrobial agents with different but complementary mechanisms of action has been shown to increase the efficacy of bacterial eradication.[8,12,26] Each treatment quadrant received 2 applications daily for 3 days, for a total of 6 applications, with the last application being applied on the morning of specimen collection. A circle measuring 3 cm in diameter was drawn at each site, and subjects were instructed to apply the topical agent within each circle using a mirror. Care was taken to separate each experimental site by at least 10 cm to avoid cross-contamination between the biopsy sites.

After an injection of approximately 3 mL of 1% lidocaine into each quadrant, a 3-mm dermal punch biopsy specimen was obtained using a commercially available kit (Acu-Punch; Acuderm, Fort Lauderdale, FL, USA). Care was taken to ensure the dermal layer was included in each biopsy specimen. The region superior to the scapular spine was chosen for all biopsy specimens because of its proximity to the shoulder, which has been shown to have high rates of *C acnes* colonization.[2,6,11] Each punch biopsy specimen was cultured anaerobically for 14 days as previously described.[2] All isolates of *C acnes* were subcultured on Brucella agar and assessed for the hemolytic phenotype at 48 hours.[17,29]

Statistical analysis

With an α of 0.05 and 80% power, a sample size of 12 subjects would be required to detect medium to large effects between the groups.[27] More specifically, our study was powered to detect at least a 50% absolute risk reduction in the rate of positive cultures between groups. This large difference was chosen because our intent was to find a treatment method that eradicates *C acnes* in the dermal layer in all subjects rather than demonstrate a marginal decrease in colonization rates. As prior studies have shown colonization rates as high as 55% to 58% using similar protocols,[6,11] our study would be powered to detect complete or nearly complete eradication of *C acnes* at these rates of colonization. The McNemar test was used to compare the proportion of positive cultures and the proportion of the *C acnes* hemolytic phenotype present in each group. Power analysis calculations were performed using G*Power (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany), and statistical analysis calculations were performed using Stata software (version 13.1 MP; StataCorp, College Station, TX, USA).

Results

Ten men and two women participated in the study. The average age was 29.4 years (range, 26-40 years), and the average body mass index was 25.0 (range, 22.3-31.0). There were no reported adverse reactions and no deviations from the assigned treatment quadrants.

C acnes grew in similar proportions in the control, BP, clindamycin, and combination topical benzoyl peroxide–clindamycin groups (Table I). No statistically significant differences in positive culture rates were noted, although the BP treatment group approached significance ($P = .0833$, Table II). No relation between age, body mass index, or sample site and positive *C acnes* growth could be identified with the numbers available. Similarly, the proportion of hemolytic positive *C acnes* cultures in each of the treatment groups was similar (Table III). No statistically significant differences in the rates of the hemolytic phenotype present were found between the groups (Table IV).

Table I Summary of culture results by treatment type

	Biopsy culture results	
	Negative, n	Positive, n (%)
NC	8	4 (33.3)
BP	11	1 (8.3)
CL	10	2 (16.7)
BPCL	10	2 (16.7)
Total	39	9 (18.7)

NC, negative control; *BP*, 5% topical benzoyl peroxide; *CL*, 1% topical clindamycin; *BPCL*, 5% topical benzoyl peroxide and 1% clindamycin.

Table III Summary of presence of hemolytic phenotype by treatment arm

	Hemolytic phenotype	
	Negative, n	Positive, n (%)
NC	10	2 (16.7)
BP	12	0 (0.0)
CL	10	2 (16.7)
BPCL	10	2 (16.7)
Total	42	6 (12.5)

NC, negative control; *BP*, 5% topical benzoyl peroxide; *CL*, 1% topical clindamycin; *BPCL*, 5% topical benzoyl peroxide and 1% clindamycin.

Discussion

To our knowledge, this is the first study to examine the efficacy of combination topical benzoyl peroxide and clindamycin to eradicate *C acnes* colonization in the dermal layer of the skin, using dermal punch biopsy specimens. Application of topical benzoyl peroxide and clindamycin was ineffective at eradicating *C acnes* in all subjects. Benzoyl peroxide alone may be effective at decreasing *C acnes* growth; however, with the numbers available, we were unable to demonstrate statistical significance. Furthermore, our hypothesis that benzoyl peroxide and clindamycin combination therapy would show the greatest efficacy was not supported by our data. Given the findings presented in this study, we believe further studies investigating the clinical role of preoperative topical antimicrobial agents are warranted.

Benzoyl peroxide and clindamycin in combination have been shown to reduce *C acnes* colonization in the dermatologic literature in several studies.[12,26] In a randomized trial examining superficial facial colonization of *C acnes*, Leyden[12] demonstrated that twice-daily application of combination benzoyl peroxide and clindamycin therapy resulted in a 91% reduction of facial *C acnes* colonization after 24 hours and 99.9% reduction by 2 weeks. This was superior to results of clindamycin monotherapy; however, the author did not include a benzoyl peroxide monotherapy treatment arm. In a meta-analysis of 23 clinical studies comparing the efficacy of benzoyl peroxide and clindamycin, Seidler and Kimball[26] demonstrated that combination therapy showed no benefit over benzoyl peroxide alone at 2 to 4 weeks but was incrementally better than benzoyl peroxide alone after 10 to 12 weeks of therapy and was significantly superior to clindamycin alone at eradicating acne lesions. Although statistical significance was achieved, the authors believed that the addition of clindamycin to benzoyl peroxide monotherapy did not result in a clinically meaningful benefit. Our results support these findings as we were unable to demonstrate a benefit with the addition of clindamycin. However, our study was not powered to detect differences between treatment arms and measured *C acnes* growth rather than facial acne lesions. Nevertheless, our findings support the dermatologic literature and do not support the use of topical clindamycin prior to shoulder surgery.

In vitro, *C acnes* is highly susceptible to antibiotic and antiseptic agents,[7,13] yet standard surgical-site preparation may fail to prevent deep infection from *C acnes*.[6,15,20,23] *C acnes* resides in and proliferates by utilization of the components of sebum, the waxy substance secreted by the sebaceous glands, which may provide a protective barrier against antimicrobial agents in vivo.[1] Prior studies have shown that male individuals have a higher prevalence of pilosebaceous glands, possibly explaining the increased prevalence of *C acnes* infections in this

Table II *P* values for positive biopsy culture results in treatment groups compared with control group

	P value for biopsy culture results*
NC vs. BP	.0833
NC vs. BPCL	.1573
NC vs. CL	.1573

NC, negative control; *BP*, 5% topical benzoyl peroxide; *BPCL*, 5% topical benzoyl peroxide and 1% clindamycin; *CL*, 1% topical clindamycin.

* *P* values were calculated using the McNemar χ^2 exact test comparing the proportion of positivity between the specified treatment group and the NC group.

Table IV *P* values for hemolytic phenotype results in treatment groups compared with control group

	P value for hemolytic phenotype results*
NC vs. BP	.158
NC vs. BPCL	>.999
NC vs. CL	>.999

NC, negative control; *BP*, 5% topical benzoyl peroxide; *BPCL*, 5% topical benzoyl peroxide and 1% clindamycin; *CL*, 1% topical clindamycin.

* *P* values were calculated using the McNemar χ^2 exact test comparing the proportion of hemolytic positivity between the specified treatment group and the NC group.

population.[9,22] This knowledge has led surgeons to investigate the efficacy of serially applied topical agents in an attempt to eradicate *C acnes* in the deeper layers of the skin.

Several clinical studies have assessed the efficacy of topical clindamycin and benzoyl peroxide prior to shoulder surgery. Sabetta et al[24] found that the use of topical benzoyl peroxide preoperatively for 48 hours reduced the growth of *C acnes* in superficial skin, intraoperative deep tissue, and synovial fluid cultures. Dizay et al[4] showed a decrease in the deep tissue *C acnes* bacterial load in a group of patients who used daily benzoyl peroxide and clindamycin combination therapy for an average of 2.3 days. Kolakowski et al[10] demonstrated that 3 daily applications of benzoyl peroxide resulted in a marked reduction in the *C acnes* bacterial load at anterior and posterior portal sites compared with daily application of chlorhexidine gluconate. They used a technique that allowed for *C acnes* quantification in the sebaceous glands, suggesting benzoyl peroxide may have the ability to penetrate deeper layers better than chlorhexidine gluconate, which has been shown in prior studies to be ineffective at eradicating *C acnes* in the dermis.[6,11] Our study suggests benzoyl peroxide monotherapy may decrease the prevalence of *C acnes* but may not eradicate *C acnes* in all subjects.

This study examined the hemolytic phenotype in patients with positive *C acnes* cultures. The *C acnes* hemolytic phenotype was eradicated in the benzoyl peroxide monotherapy group, suggesting topical benzoyl peroxide alone may be an effective strategy at targeting this phenotype. Previous literature suggested that hemolytic phenotypes of *C acnes* may be more virulent[17] and more antibiotic resistant particularly to clindamycin.[29] However, recently, Mahylis et al[14] found no association between the *C acnes* hemolytic phenotype and infection and concluded that hemolysis does not increase pathogenicity. Given the differing reports in the literature, the clinical relevance of our results regarding the hemolytic phenotype remains to be determined.

The relatively small sample size and low positive culture rate in our negative control group may be viewed as limitations of our study as this limited our ability to detect differences between the treatment arms and negative control. Prior studies have demonstrated a 55% to 58% colonization rate in healthy subjects[6,11]; however, only 33% of the negative controls demonstrated colonization of *C acnes* within the dermis in our study, limiting the magnitude of our detectable effect size and our ability to detect differences between treatment arms. However, the goal of our study was to demonstrate complete eradication of *C acnes* using a topical agent, not to detect an intergroup difference. As such, this study was still able to demonstrate that no topical antimicrobial was able to prevent *C acnes* growth in all subjects, a finding that is noteworthy particularly for shoulder arthroplasty surgeons. The lack of a pure negative control group to determine false-positive culture rates is another limitation of our study; however, all samples were collected by the same 2 authors (N.H. and K.S.H.) using an identical protocol in an attempt to control for possible sampling error. Despite these limitations, this study provides valuable information about the continued presence of *C acnes* in the dermal layer of the skin in a subset of healthy subjects despite the use of several commercially available topical antimicrobial agents.

Conclusion

The serial application of clindamycin and benzoyl peroxide failed to completely eradicate *C acnes* from the dermal layer of the skin in all subjects. Further clinical studies are warranted to determine the role of topical antimicrobial therapy in reducing *C acnes* infections following shoulder surgery.

Disclaimer

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