Efficacy of Blue Light Therapy In Reducing Cutibacterium Acnes Bioburden at the Deltopectoral Interval

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Efficacy of Blue Light Therapy In Reducing Cutibacterium Acnes Bioburden at the Deltopectoral Interval

Short Title: Blue Light Therapy Shoulder

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A: Specific Aims

Aim 1: To determine if blue light therapy is superior to 5% topical benzoyl peroxide gel in eradicating *Cutibacterium Acnes* at the deltopectoral interval of the shoulder

Aim 2: To determine if blue light therapy has additive or synergistic effects in eradicating *Cutibacterium Acnes* in conjunction with 5% topical benzoyl peroxide gel at the deltopectoral interval.

Hypothesis: Blue light therapy will result in fewer positive culture specimens than those treated with topical benzoyl peroxide for *Cutibacterium Acnes*

B: Purpose

Infection after shoulder surgery leads to significant morbidity to patients and puts significant strain on the healthcare system. As the case volume of shoulder arthroplasties continues to rise, the importance of minimizing infection rises in concert. The purpose of this study is to determine if blue light therapy, used commonly in dermatologic practice, is as effective as or more effective

than 5% topical benzoyl peroxide gel in reducing the incidence of positive cultures for *Cutibacterium Acnes.*

C: Background & Significance

Cutibacterium Acnes (C. Acnes), formerly known as *Propionibacterium Acnes,* is a common pathogen leading to infection following shoulder surgery.[1,2] *P. Acnes* a gram-positive, facultative anaerobic rod that resides in the pilosebaceous ducts of the skin and has a predilection for colonizing the skin of human shoulders more frequently than at the hip or knee region.[3-6] A recent investigation characterizing the shoulder microbiome reported no evidence of *C. Acnes* in any subdermal tissues including subcutaneous fat, rotator cuff tendon, joint capsule, and cartilage indicating *C. Acnes* is solely a skin flora.[7] Surgical site infection can be a devastating complication of shoulder surgery, particularly arthroplasty surgery, leading to pain, future surgeries, and significant health care costs.[1,8] In revision shoulder arthroplasty cases, *C. Acnes*, has been identified as one of the most common pathogens with rates ranging from 19% to 70% of cases performed for prosthetic joint infection (PJI).[8-12] Risk factors for infection after shoulder surgery, including *C. Acnes,* includes male gender, increased duration of surgery, and being the first surgery of the day.[8,13,14] *C. Acnes* infections are oftentimes challenging to diagnose, grow slowly in culture, require debridement, revision of implants, and prolonged antibiotic courses to clear from shoulder arthroplasties.[7,15] Revision incisions through colonized skin may produce seeding of *C. Acnes* into the dermis and subcutaneous tissue. These deeper infections evade pre-operative eradication and can lead to functional immobility and chronic pain.[16,17]

In recent years, topical methods of eradicating or reducing the skin burden of *C. Acnes* have been investigated, including chlorhexidine swabs and topical benzoyl peroxide (BPO) as oral antibiotics including doxycycline have not proven effective.[2,3,18-22] Topical BPO has been shown in several studies to be superior to chlorhexidine in reducing bacterial load using swab cultures of the epidermis and deep sebaceous glands.[2,3] However, several drawbacks of topical BPO have been described including bleaching of clothing, requirement for serial application leading to poor compliance, potential for irritant and allergic contact dermatitis, and inconsistency in eradicating *C. Acnes* in some reports.[23] In addition, there is concern that topical treatments may not penetrate into the superficial dermal layers to eradicate bacteria colonizing 1 mm beneath the skin surface, where the sebaceous glands reside.[24]

Blue light therapy, with wavelength 405nm-470 nanometers (nm), is an Food & Drug Administration (FDA) approved modality that has previously been described in the dermatology literature as a highly effective antimicrobial agent against *C. Acnes,* among other bacteria, in mild to moderate inflammatory acne patients.[25-29] The benefit of blue light therapy is that a single treatment can kill 99.9% of *C. Acnes.*[30-32] The anti-microbial mechanism of action involves absorption by endogenous porphyrins which induce generation of reactive oxygen species leading to cell death and DNA cleavage. In contrast to topical antimicrobials, blue light therapy penetrates to 1.2-1.5 mm beneath the skin surface to eliminate bacteria residing in the sebaceous glands.[33,34] Blue light demonstrates bactericidal effects at doses as low as 5 J/cm^2, while higher doses (>100 J/cm^2) are necessary to injure human tissues.[29,32,35] Wavelengths of 405-415 nm with a radiant exposure of 54 - 75 J/cm^2 have been demonstrated to exert the greatest antimicrobial effects against *C. Acnes.*[30,32] Variables that affect radiant exposure include: power of the blue light device (W), desired surface area to be treated (cm^2), time duration of treatment (s). Devices with lower irradiances (W/cm^2) require treatment for a longer time duration (s) to

achieve adequate radiant exposure [energy (J)/area (cm^2)] for antimicrobial effects. Side effects of blue light are transient and mild, including dry skin and hyperpigmentation.

This proposal aims to investigate a novel light-based treatment to reduce morbidity in shoulder surgical patients. This has potential to improve outcomes and reduce health care utilization associated with infectious complications of shoulder arthroplasty.

Limitations:

- This study is not without limitations. *C. Acnes* is challenging to culture with samples needing to be held for approximately 2 weeks to ensure 95% sensitivity.[36,37] In addition, there is no standard method for swabbing the skin to obtain cultures. There have been various methods described for how to swab technique when obtaining culture samples.[3,19,38] The methodology used by Scheer et al was selected for the present study given the detailed description and was therefore, reproducible.[3]

Future Directions:

- Subsequent investigations to evaluate the efficacy of blue light therapy for eradication of *C. Acnes* will include a randomized clinical trial in shoulder arthroplasty patients incorporating not only superficial cultures but deep cultures and synovial fluid analysis.[39]
- Additional studies targeting the highest risk surgical patient population, revision arthroplasty cases, will be impactful. These studies should incorporate 2-year clinical follow-up complete with patient reported outcome measures to see if utilization of blue light therapy may be associated with diminished pain and dysfunction in those patients with culture negative work-up.
- Finally, blue light studies to date indicate promising applications beyond *C. Acnes* including activity against staph, strep, pseudomonas, and yeast. Future studies could focus on these species as sources of both prosthetic join infection as well as blue light's role in treatment and preventing infection across multiple specialties.[40]

D: Preliminary Studies/Progress Report

No preliminary studies have been conducted to date. This study will begin enrolling in July 2020 once the purchasing of all materials has transpired and all funding sources in addition to internal funding are secured.

E: Research Design and Methods

Study Design: Single-Blinded (investigators performing analysis), randomized controlled trial

Study Participants/Human Subjects: 60 volunteers

Power Analysis: Power analysis calculations were performed using G*Power (Universität Kiel, Germany). With an α of 0.05 and 90% power to detect a 50% difference in positive culture rates as previously described,[2,20] it was determined that 51 total patients needed to be enrolled. For the purposes of the present study, assuming a 15% attrition rate, it was determined that 20 subjects per group, 60 subjects total, were necessary.

Inclusion Criteria: Healthy Male Volunteers at least 18 years of age

Exclusion Criteria:

- Allergy to benzoyl peroxide or chlorhexidine
- <18 years of age
- Female Gender
- Previous history of shoulder infections
- Antibiotics taken within one month of research visit
- Immunocompromised state
- Active cancer
- Diabetes
- Skin lesions or abrasions over the deltopectoral interval
- Topical corticosteroid treatment to either shoulder or systemic corticosteroid treatment within 2 weeks of research visit
- Topical benzoyl peroxide treatment to either shoulder within 2 weeks of research visit
- Blue light therapy treatment to either shoulder within 2 weeks of research visit
- Prior incision over the deltopectoral interval of either shoulder
- Contraindication to blue light treatment

Demographics Collected: An intake form will be distributed to each subjected consented to participate in the study. Demographics to be obtained include: age, height, weight, profession, race, medical comorbidities, surgical history, and showering habits.

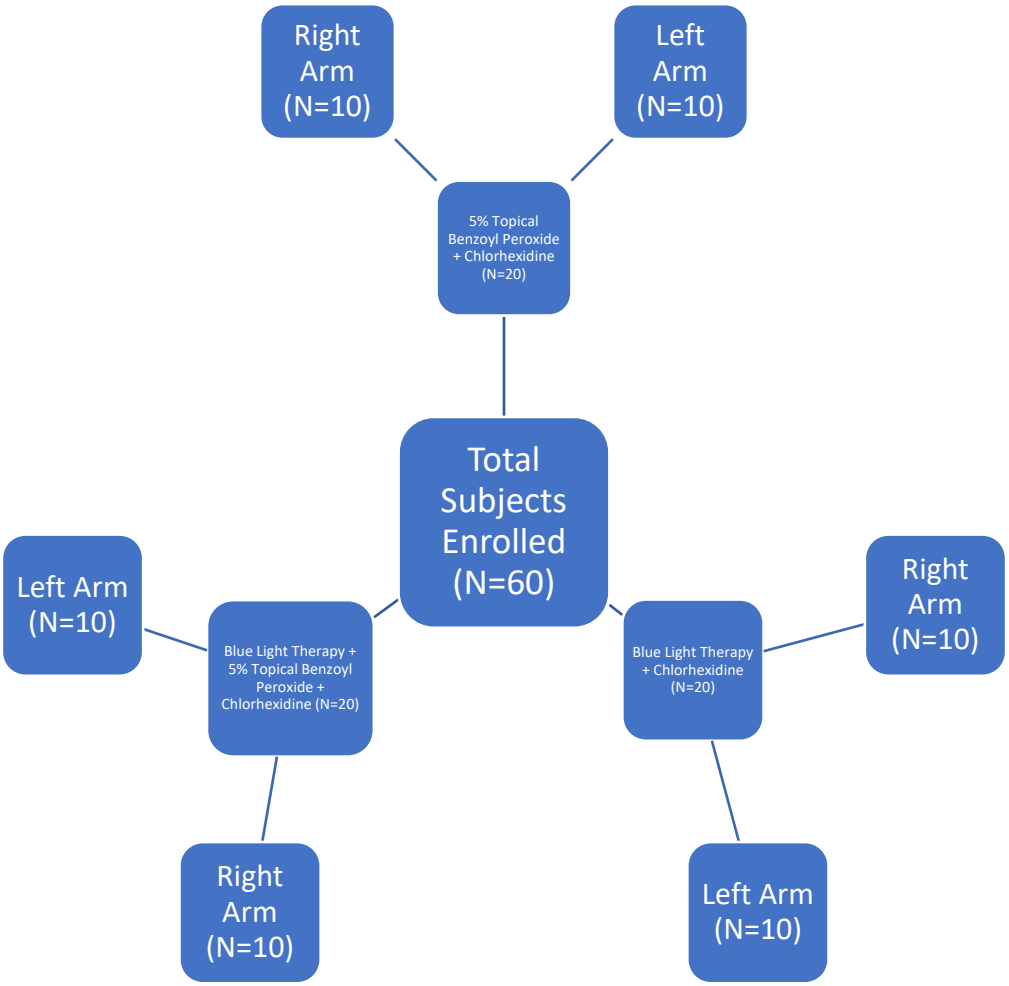
At the final research visit, subjects will be asked questions regarding their experience with the treatment they were assigned to on a Likert Scale. The subjects will also be asked regarding their satisfaction with the treatment they received, as well as a set of "would you rather" hypothetical questions regarding their preference of pre-operative experience.

Randomized Groups:

- N=20
    - 5% Topical Benzoyl Peroxide Gel + 2% Chlorhexidine Gluconate with 70% Isopropyl Alcohol. Contralateral shoulder serving as control (2% Chlorhexidine Gluconate with 70% Isopropyl Alcohol only)
- N=20
    - Blue Light Therapy + 2% Chlorhexidine Gluconate with 70% Isopropyl Alcohol. Contralateral shoulder serving as control (2% Chlorhexidine Gluconate with 70% Isopropyl Alcohol only)
- N=20
    - 5% Topical Benzoyl Peroxide Gel + Blue Light Therapy + 2% Chlorhexidine Gluconate with 70% Isopropyl Alcohol. Contralateral shoulder serving as control (2% Chlorhexidine Gluconate with 70% Isopropyl Alcohol only)
- In addition to randomizing subjects to one of the 3 above groups, subjects will be randomized to have either their right or left arm as the "treatment" arm with the contralateral serving as control. Within each group of 20 subjects, 10 will be randomized to having the right arm as the "treatment" arm and 10 will be randomized to having the left arm as the "treatment" arm.
    - Randomization will be performed using concealed envelopes to be picked at random once a subject is consented for participation in the study.

- The research coordinator consenting subjects and coordinating the blue light treatment will not be blinded given their involvement. The remainder of the research team will be blinded to both treatment arm as well as which side (left or right) served as the control.

- **Figure 1** below details the 3 separate groups that subjects could be randomized to. Each of the 3 groups will contain 20 subjects. Within each of the 3 groups, subjects will be randomized to having either the right or the left arm being the treatment arm. The treatment arm means that arm will receive either 5% topical benzoyl peroxide, blue light therapy, or both. The contralateral shoulder will be the control for each subject.



Treatment Description:

- 5% Topical Benzoyl Peroxide Gel: A pea-sized amount, ~0.5 grams, will be applied to a 10cm strip over the deltopectoral interval beginning the morning 48 hours prior to schedule research visit to obtain cultures. The benzoyl peroxide will be applied on dry skin after a shower. The gel will be applied once in the morning and once in the evening for two consecutive days as well as the morning of the scheduled research visit. Following treatment, both the treatment shoulder and control shoulder will be sterilely prepped with 2% chlorhexidine gluconate solution with 70% isopropyl alcohol and allowed to dry for 3 minutes. Following chlorhexidine preparation, a single set of cultures will be obtained from each shoulder.

- Blue Light Therapy: FDA cleared blue light product, Omniluxblue (Globalmed Technologies, Glen Elen, CA), which emits a 415 nm blue light irradiance of 40mW/cm^2 was used.[41] This product has been shown to be safe and effective.[41] The dimensions of the LED light active area is 6 inches x 14 inches, which completely covers the anterior shoulder. To achieve the radiant exposure of 54 J/cm^2 necessary for previously published antimicrobial effects against *C. Acnes*, 23 total minutes of treatment time (1,380 seconds) will be necessary (achieving a total radiant exposure of 55.2 J/cm^2). Following the application of blue light protective eyewear, the blue light therapy device will be centered over the deltopectoral interval according to device standardized use instructions and a 23-minute treatment will be administered to dry skin. As was done in the topical BPO group, following treatment, both the treatment shoulder and control shoulder will be sterilely prepped with 2% chlorhexidine gluconate solution with 70% isopropyl alcohol and allowed to dry for 3 minutes. Following chlorhexidine preparation, a single set of cultures will be obtained from each shoulder. Research subjects and research personnel conducting the blue light treatments will be wearing medical grade blue light protective glasses for safety.

- For the subjects randomized to both blue light therapy and 5% topical benzoyl peroxide gel: 5% topical benzoyl peroxide treatment will be performed on dry skin immediately after a shower as described in the above paragraph. Again, five total treatments will be performed prior to research visit. On the day of the research visit, the blue light therapy protocol described above will be performed exactly the same followed by culture obtainment.

Culture:

- Each research participant will have skin swab cultures obtained after the completing the assigned treatment. The method described by Scheer et al to obtain the skin swab cultures will be utilized. Specifically, all skin swabs will be taken by rubbing 15 times over a 10 cm deltopectoral interval.[3] Cultures will be sent for both aerobic and anaerobic growth with speciation.
- Our previous protocol detailed that the main laboratory for the University of Wisconsin Hospital & Clinics located at 600 Highland Ave was to be used to run all skin swab culture and speciation for this study. Due to inflexibility in protocols and significant costs, we have elected to utilize the academic microbiology laboratory of Dr. Nasia Safdar, MD, PhD. Dr. Safdar is a full professor, attending faculty in the department of infectious disease and microbiology at the University of Wisconsin School of Medicine

and Public Health. She maintains a research laboratory staffed by several graduate and post-graduate individuals located at both the University of Wisconsin Hospitals & Clinics as well as a second space at the William S. Middleton Memorial Veterans Hospital.

- The culture protocol previously published by Kolakowski et al[1] was used with few exceptions. Following swab collection, the swab culture tips were broken at a breakpoint into to individual 4 mL tubes containing 2 mL of Letheen broth and placed into a biohazard bag. Samples contained in biohazard bags will be placed into a pre-chilled insulated cooler and transported within 4 hours to our microbiology laboratory. In the lab, sample tubes containing swab tips were individually removed from the pre-chilled insulated cooler and vortexed to mix well. Two hundred microliters (µL) of sample were transferred to a 5 mL Falcon tube containing 1.8 mL of 0.05% Tween-80 in water and mixed well (dilution 1). Dilution 2 will be prepared by transferring 200 µL of dilution 1 to a 5 mL Falcon tube containing 1.8 mL of 0.05% Tween-80 in water and mixing well. Dilution 3 will be prepared by transferring 200 µL of dilution 2 to a 5 mL Falcon tube containing 1.8 mL of 0.05% Tween-80 in water and mixing well. Dilution 4 will be prepared by transferring 200 µL of dilution 3 to a 5 mL Falcon tube containing 1.8 mL of 0.05% Tween-80 in water and mixing well.
- Spot plates will be prepared in duplicate by transferring 50 µL of the original sample and each dilution (a total of 5 spots for each plate) to a Brucella agar plate. Sample solutions will be allowed to dry on the agar plate and then transferred to an anaerobic environment and allowed to incubate at 37 °C for 7 days. After 7 days of incubation, plates will be checked for growth and spot dilutions that can be read will be counted. Presumptive positive colonies will be subbed to Brucella agar for additional workup (gram stain, catalase test, and indole test. Presumptive positive samples will have a crude PCR lysate made and will be undergo a confirmatory 16s PCR test. We will be obtaining a virulent strain of *C. Acnes* was obtained and how we used that as gold standard methodology.

C. acnes Culture Banking

- If *C. acnes* does grow for a tissue culture, we plan to bank a colony of the bacterium for potential use in a future study. There is no added risk to research subjects as no additional cultures are taken. The banked samples will simply be a colony of growth from the culture media for storage for possible future use. At this time, there are no planned uses for these samples. Colonies of *C. acne*s banked samples will be de-identified and labeled with a simple subject number as the culture swabs are when they are collected. Recent literature suggests there are different sub-species of *C. acnes* with difference virulence, it may be worth pursuing a bench research study in the future where these banked colonies of C. acnes are sub-speciated and subjected to a variety of anti-microbial measures to try and determine which strains are more challenging to eradicate.
- We would like to bank the samples for 5 years from the date of study completion after which time the samples will be destroyed.

Timeline:

- Anticipated enrollment and data collection: July 2020-December 2020
- Data Analysis and Manuscript Preparation January 2021-March 2021

F: Human Subjects

The associated human subjects protocol for this project is currently in review with our Health Sciences Internal Review Board.

G: Vertebrae Animals

Not Applicable

H: Literature Cited

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