ABSTRACT

Introduction: Propionibacterium acnes is a gram-positive anaerobe that is found on the dermis and epidermis of the shoulder and is the most commonly identifiable cause of periprosthetic shoulder joint infection. Various topical strategies have been investigated to reduce the prevalence of P. acnes, with several demonstrating efficacy in reducing the positive culture. The aim of this systematic review and meta-analysis is to review the literature to assess the effectiveness of topical preparations in reducing the prevalence of P. acnes in shoulder surgery.

Methods: The study protocol was designed and registered prospectively on PROSPERO (International prospective register for systematic reviews). Databases used for the literature search will include MEDLINE, EMBASE, PsycINFO, and The Cochrane Library. Randomised controlled trials (RCTs) evaluating the use of any topical preparation against placebo, in all types of shoulder surgery, will be included. Our primary outcome is the number of colony forming units of P. acnes. Secondary outcomes will include adverse events such as skin irritation, wound dehiscence, and the incidence of revision surgery due to infection. The Cochrane Risk of Bias Tool 2.0 and Jadad score will be used to assess the quality of methodology of the studies. Statistical analysis will be used to assess inconsistency and bias across included studies. Comparable outcome data will be pooled and analysed quantitatively or qualitatively as appropriate.

Ethics and dissemination: No ethical clearances required for this study. This systematic review and meta-analysis will be published in a peer-reviewed journal.

Highlights

- Various topical strategies have been investigated to reduce the prevalence of P. acnes, the most common identifiable cause of periprosthetic shoulder joint infection, with several demonstrating efficacy in reducing the positive culture.
1. INTRODUCTION

Propionibacterium (also Cutibacterium) acnes is an anaerobic, gram-positive bacterium that inhabits the sebaceous glands of the skin and sebum-rich hair follicles [1]. There is an increased prevalence of P. acnes found on the shoulder and its surrounding regions due to the increased number of hair follicles and sebaceous glands, and there is therefore a higher prevalence of P. acnes culture on the shoulder than other common orthopaedic surgical sites such as the knee or hip [1–3]. P. acnes is found in both the epidermal and dermal layers of the skin and is one of the most common causative pathogens of postoperative infection in open shoulder surgery [4]. Data is however limited on the incidence of P. acnes infection in shoulder arthroscopy. A significant proportion of patients undergoing shoulder surgery have a positive skin and/or joint culture for P. acnes, and a small proportion of these patients go onto develop a postoperative P. acnes infection [5]. P. acnes is the most commonly identifiable cause of periprosthetic joint infection, with literature reporting positive culture rates between 20%–70% [6, 8]. Other microorganisms found to be responsible for periprosthetic joint infections include; high-virulent pathogens in early infections – Staphylococcus aureus, streptococci, and enterococci – and low-virulent organisms in delayed infections – coagulase-negative staphylococci or cutibacterium species [9].

Various topical strategies have been studied to reduce the prevalence of P. acnes on the shoulder girdle before surgery, such as benzoyl peroxide, topical antibiotics such as clindamycin phosphate, chlorhexidine gluconate and Betadine (Purdue Pharma LP, Stamford, CT, USA) [7, 8, 10–13]. Betadine and chlorhexidine gluconate have been shown to be ineffective at reducing the prevalence of P. acnes at the surgical site [13]. This is most likely because these specific topical preparations cannot reach the sebaceous glands, and once a skin incision is made, P. acnes can enter the surgical wound.

Benzoyl peroxide (BPO) is a bactericidal agent commonly used for treating acne vulgaris and has been shown in multiple randomised studies to reduce the prevalence of P. acnes on the shoulder [10–12, 14]. Application of 5% BPO three days prior to surgery has been shown to effectively reduce P. acnes culture [11, 12, 14]. There is however an issue of patient compliance with this particular management as some patients can experience mild pruritus when using 5% BPO [14–16]. Moreover, the combination of 5% BPO with 1.2% clindamycin phosphate gel has also been shown to reduce P. acnes colonisation [8]. Most recently, hydrogen peroxide, the active agent in BPO, has been shown to reduce P. acnes in patients undergoing arthroscopic shoulder surgery, but dermal application after skin incision does not significantly reduce the prevalence of P. acnes during shoulder arthroplasty [7, 13].

The aim of this systematic review and meta-analysis is to evaluate the use and outcomes of topical treatments to reduce P. acnes prevalence in shoulder surgery. Our primary outcome will be the number of colony forming units (CFU). Secondary outcomes will include adverse events related to both infection and application of topical preparations, such as skin irritation, wound dehiscence, and the incidence of revision surgery due to infection.

2. METHODS

This study protocol was designed and registered prospectively on the PROSPERO (International prospective register for systematic reviews) database (Ref: CRD42022310312) [17]. The protocol is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocol (PRISMA-P) [18, 19].

2.1. ELIGIBILITY CRITERIA

2.1.1. Study design

Only randomised controlled trials will be included. All other trial designs will be excluded.

2.1.2. Participants

We will include studies with humans of any age undergoing any type of surgery to the shoulder. This will include both arthroscopic and open techniques. Example open procedures may include shoulder arthroplasties and the Latarjet procedure. Example arthroscopic procedures may include diagnostic arthroscopies and rotator cuff repairs.
2.1.3. Intervention and comparators
The intervention of interest is any topical treatment or preparation for the reduction of *P. acnes*. We will include all individual methods of timing, dose, and area of application. The comparator can include any form of placebo or no treatment.

2.1.4. Outcomes
The primary outcome of interest will be the number of colony forming units (CFU) of *P. acnes*. Other measures of infection such as total viable counts (CFU/ml) may also be included.

Secondary outcomes examined will include adverse events related to infection and application of topical preparations, such as skin irritation, wound dehiscence, and the incidence of revision surgery due to infection.

2.1.5. Timing
No restrictions regarding timing of the study.

2.1.6. Setting
No restrictions regarding setting of the study.

2.1.7. Language
Studies of all languages will be included. Any titles requiring translation into English will be included in the appendix.

2.2. INFORMATION SOURCES
Our search strategy involved the following bibliographic databases; MEDLINE, EMBASE, PsycINFO and The Cochrane Library. The search strategy will be carried out and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis literature search extension (PRISMA-S) \[20\].

2.2.1. Search strategy
No restrictions will be placed on publication date or language. Randomised controlled trial filters from the Cochrane group will be used to increase precision and sensitivity when searching. Utilised search terms are included in the appendix. References from published systematic reviews investigating the same or similar topic will also be manually searched for relevant included studies. On searching the PROSPERO database, no ongoing or recently completed systematic reviews on this topic were found.

2.3. STUDY RECORDS
2.3.1. Data management
All literature search results will be combined and collected in Endnote X9 (Clarivate Analytics), and duplicate articles will be removed. The titles and abstracts from returned search results will be screened by two independent reviewers. This process will be conducted independently, and consensus will be sought prior to full text review. The final inclusion will then be determined by a full text review of articles that meet all eligibility criteria.

2.3.2. Data collection process
Data extraction will involve two independent reviewers: one reviewer will extract data using a standardised proforma, and the second reviewer will check the extracted data for inaccuracies. Any discrepancies in data extraction will be resolved by discussion and the involvement of a third reviewer as needed. Should there be any unclear or missing data, or any required additional information needed, we will attempt to contact individual study authors. Data capture will be organised on Microsoft Excel and Review Manager (RevMan version 5.3) used as a software tool for data management.

2.3.3. Data items
Data extraction will include study design, patient cohort, study characteristics, the topical preparation, dose and timing of application, control group intervention, primary outcome measures, and any secondary outcome measures. Mean and standard deviations will be extracted for all outcome measures. Data on adverse events will also be extracted.

2.4. OUTCOMES AND PRIORITISATION
2.4.1. Primary outcome
The primary outcome of interest will be the number of CFUs of *P. acnes*. Other outcome measures relevant to positive culture growth in vitro will also be included.

2.4.2. Secondary outcomes
Secondary outcomes examined will include adverse events related to both infection and application of topical preparations, such as skin irritation, wound dehiscence, and the incidence of revision surgery due to infection.

2.5. RISK OF BIAS OF INDIVIDUAL STUDIES
To assess individual studies for potential bias, the Cochrane collaboration Risk of Bias tool will be used \[21\]. Five domains are used to categorise bias, with a level of risk is assigned to each domain (high risk, low risk, or some concerns). Within each domain, signalling questions will be posed to guide interpretation of bias. An overall risk of bias is then generated for each study. The Jadad scale will also be used as an additional method for assessing bias \[22\]. A maximum of five points can be given by the Jadad scale. A maximum of two points can be given for randomisation – a point can be given for a study being randomised and a further point if an appropriate method of randomisation is used. Two points can be given for blinding – a point if the study has stated the use of blinding and a further point if an appropriate
method of blinding is used. If all patients involved in the trial have been accounted for, a final point is awarded.

2.6. DATA SYNTHESIS

2.6.1. Quantitative synthesis
A forest plot will be used to synthesise data related to culture of $P$ acnes if the method in which they were recorded is comparable. Standardised mean differences and inverse variance statistical analysis will be used to summarise continuous variables, such as colony forming units. Heterogeneity is expected between studies; hence a random effects model will likely be used for analysis. The chi-square test and $I^2$ statistic will be used to quantify heterogeneity. Any dichotomous data presented will be measured for effect using odds ratios. Review Manager (RevMan version 5.3) will be used as a software tool for data management and statistical analysis.

2.6.2. Qualitative synthesis
Data will be reported descriptively if outcome measures are not comparable across studies, the heterogeneity is too high, or the incidence rate is too low for pooled statistical analysis.

2.6.3. A priori subgroup analyses
There are no predetermined subgroup analyses. Subgroup analyses may be possible based on the topical treatment used, as well as, the method of timing, dose, and area of application.

2.6.4. Meta-bias
A funnel plot will be used to assess publication bias of included studies investigating our primary outcome. Selective reporting will be assessed by reviewing any available trial registrations or trial protocols to compare the pre-defined intended outcomes with those analysed and reported in the final manuscript. The risk of bias for each study will be assessed as previously described. To measure inconsistency, a statistical analysis of heterogeneity will be used to assess bias across studies.

2.6.5 Confidence in cumulative estimate
The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to assess the strength of the body of evidence [23–25]. Outcomes will be assessed as being of very low, low, moderate, or high certainty.

APPENDIX

Search terms for MEDLINE
1. Randomised.ab,ti
2. Placebo.ab,ti
3. Randomly.ab,ti
4. Trial.ti
5. Clinical trial.mp
6. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
7. Shoulder.ab,ti
8. Procedure.ab,ti
9. Surgical.ab,ti
10. Repair.ab,ti
11. Reconstruction.ab,ti
12. Operative.ab,ti
13. Operation.ab,ti
14. Arthroplasty.ab,ti
15. Arthroscop*.ab,ti
16. Glenohumeral.ab,ti
17. Glenoid.ab,ti
18. Humerus.ab,ti
19. Humeral.ab,ti
20. Acromioclavicular.ab,ti
21. Acromion.ab,ti
22. Coracoid.ab,ti
23. Scapula.ab,ti
24. 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27
25. 29 OR 30 OR 31 OR 32
26. Topical.ab,ti
27. Betadine.ab,ti
28. Povidone-iodine.ab,ti
29. Iodopovidone.ab,ti
30. Iodophor.ab,ti
31. Chlorhexidine.ab,ti
32. CHG.ab,ti
33. Isopropyl alcohol.ab,ti
34. ChloraPrep.ab,ti
35. DuraPrep.ab,ti
36. Benzoyl peroxide.ab,ti
37. BPO.ab,ti
38. Hydrogen peroxide.ab,ti
39. Sterile.ab,ti
40. 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47
41. 8 AND 28 AND 33 AND 48

COMPETING INTERESTS
The authors have no competing interests to declare.
AUTHOR CONTRIBUTIONS

All authors contributed equally to this work.

All authors have read instructions to authors.

All authors have seen and agreed to the submitted version of the paper.

The material included is original and has not been published elsewhere or submitted for publication simultaneously.

If this protocol is accepted for publication, it will not be published elsewhere in the same form, in English or in any other language, without written consent of the copyright holder.

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REFERENCES

1. Achermann Y, Goldstein EJC, Coenye T, Shirliff ME. Propionibacterium acnes: from Commensal to Opportunistic Biofilm-Associated Infectious Pathogen. *Clinical Microbiology Reviews*. 2014; 27(3): 419–40. DOI: https://doi.org/10.1128/CMR.00092-13

2. Patel A, Colfee RP, Plante M, Fischer SA, Green A. Propionibacterium acnes colonization of the human shoulder. *J Shoulder Elbow Surg*. 2009; 18(6): 897–902. DOI: https://doi.org/10.1016/j.jse.2009.01.023

3. Athwal GS, Sperling JW, Rispoli DM, Cofield RH. Deep infection after rotator cuff repair. *J Shoulder Elbow Surg*. 2007; 16(3): 306–11. DOI: https://doi.org/10.1016/j.jse.2006.05.013

4. Achermann Y, Soinin R, Schwzyer H. et al. Characteristics and outcome of 16 periprosthetic shoulder joint infections. *Infection*. 41: 613–620 (2013). DOI: https://doi.org/10.1007/s15010-012-0360-4

5. Belk JW, Kraeutler MJ, Smith JR, Littlefield CP, Bravman JT, Houck DA, et al. Prevention of Cutibacterium acnes infection in arthroscopic shoulder surgery: a systematic review. *J Shoulder Elbow Surg*. 2020; 29(5): 867–73. DOI: https://doi.org/10.1016/j.jse.2019.12.032

6. Mook WR, Klement MR, Green CL, Hazen KC, Garrigues GE. The Incidence of Propionibacterium acnes in Open Shoulder Surgery: A Controlled Diagnostic Study. *JBJS*. 2015; 97(12): 957–63. DOI: https://doi.org/10.2106/JBJS.N.00784

7. Grewal G, Polisetty T, Boulch A, Colley R, Topia R, Levy JC. Does application of hydrogen peroxide to the dermis reduce incidence of Cutibacterium acnes during shoulder arthroplasty: a randomized controlled trial. *J Shoulder Elbow Surg*. 2021; 30(8): 1827–33. DOI: https://doi.org/10.1016/j.jse.2021.03.144

8. Dizay HH, Lau DG, Nottage WM. Benzoyl peroxide and clindamycin topical skin preparation decreases Propionibacterium acnes colonization in shoulder arthroscopy. *J Shoulder Elbow Surg*. 2017; 26(7): 1190–5. DOI: https://doi.org/10.1016/j.jse.2017.03.003

9. Izakovicova P, Borens Q, Trampuz A. Periprosthetic joint infection: current concepts and outlook. EFORT Open Reviews. 2019; 4(7): 482–494. DOI: https://doi.org/10.1302/2058-5241.14.180092

10. Sabetta JR, Rona VP, Vodasdi KB, Greene RT, Cunningham JG, Miller SR, et al. Efficacy of topical benzoyl peroxide on the reduction of Propionibacterium acnes during shoulder surgery. *J Shoulder Elbow Surg*. 2015; 24(7): 995–1004. DOI: https://doi.org/10.1016/j.jse.2015.04.003

11. Scheer VM, Bergman Jungestrom M, Lerm M, Serrander L, Kalen A. Topical benzoyl peroxide application on the shoulder reduces Propionibacterium acnes: a randomized study. *J Shoulder Elbow Surg*. 2018; 27(6): 957–61. DOI: https://doi.org/10.1016/j.jse.2018.02.038

12. Kolakowski L, Lai JK, Duvall GT, Jauregui JJ, Dubina AG, Jones DL, et al. Neer Award 2018: Benzoyl peroxide effectively decreases preoperative Cutibacterium acnes shoulder burden: a prospective randomized controlled trial. *J Shoulder Elbow Surg*. 2018; 27(9): 1539–44. DOI: https://doi.org/10.1016/j.jse.2018.06.012

13. Stull JD, Nicholson TA, Davis DE, Namdari S. Addition of 1% hydrogen peroxide to standard skin preparation reduces Cutibacterium acnes-positive culture rate in shoulder surgery: a prospective randomized controlled trial. *J Shoulder Elbow Surg*. 2020; 29(2): 212–6. DOI: https://doi.org/10.1016/j.jse.2019.09.038

14. Bikowski J. A review of the safety and efficacy of benzoyl peroxide (5.3%) emollient foam in the management of truncal acne vulgaris. *J Clin Aesthet Dermatol*. 2010; 3(11): 26–29.

15. Brandstetter AJ, Maibach HI. Topical dose justification: benzoyl peroxide concentrations. *Journal of Dermatological Treatment*. 2013; 24(4): 275–7. DOI: https://doi.org/10.3109/09546634.2011.641937

16. Leyden JJ. Efficacy of benzoyl peroxide (5.3%) emollient foam and benzoyl peroxide (8%) wash in reducing Propionibacterium acnes on the back. *J Drugs Dermatol*. 2010; 9: 622–625.

17. Sewpaul Y, Rashid M, Leung B, Hartland AW, Navar S. Topical treatments in reducing Propionibacterium acnes infection in shoulder surgery – a systematic review.
