**STUDY PROTOCOL:**

**STUDY TITLE: The efficacy of topical preparations in reducing the incidence of P. Acnes in total shoulder arthroplasty**

**ABBREVIATED TITLE: The efficacy of topical preparations in reducing the incidence of P. Acnes in total shoulder arthroplasty**

PROJECT SUMMARY

The primary aim of this project is to determine the efficacy of 3 different topical preparations in the eradication of P. Acnes contamination during primary total shoulder arthroplasty.

Null Hypothesis statement: Topical benzoyl peroxide (5%) with clindamycin (1%) is of equal or lesser effectiveness compared to benzoyl peroxide (5%) or pHisohex (1% triclosan, sodium benzoate 5mg/mL benzyl alcohol 5mg/mL) wash in eradication of P. Acnes contamination in primary total shoulder arthroplasty.

**STUDY IDENTIFICATION**

Registered with xxxx

Registered by xxxx

**SPONSOR**

None

**ADMINISTERING INSTITUTION**

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GLOSSARY OF ABBREVIATIONS AND TERMS:

Proprionbacterium acnes – *P. Acnes*

# Total shoulder arthroplasty – TSA

Prosthetic joint infection – PJI

RATIONALE AND BACKGROUND INFORMATION

Total shoulder arthroplasty (TSA) is a common and effective orthopaedic procedure for the treatment of osteoarthritis of the shoulder as well as in management of fracture and rotator cuff pathology (Ricchetti et al, 2011, Australian National Joint Registry, 2016)**.** The number of arthroplasty procedures undertaken each year in Australia continues to increase; in 2016 a total of 5757 shoulder arthroplasty procedures took place, a 10.2% increase from the previous year and a 218% increase from 2008 (Australian National Joint Registry, 2016).

Prosthetic joint infection (PJI) remains a common cause of surgical revision accounting for 6.1% of anatomical total shoulder arthroplasty (aTSA) and 18% of reverse total shoulder arthroplasty (rTSA**)** (Australian National Joint Registry, 2016). Common pathogenic organisms involving procedures of the shoulder include *Staphylococcus spp*. and *Propionbacterium Acnes* (*P. Acnes*) (Patel et al, 2009). Due to the increasing number of procedures performed, the process by minimising post-operative infection and associated complications through low-cost, simple implemented methods is of utmost importance.

Over the past decade, *P. Acnes* has become increasingly recognised as a causative infective pathogen following procedures of the shoulder joint (Falconer et al 2016, Levy et al 2013). Retrospective analysis of revision shoulder arthroplasty has found *P. Acnes* positive cultures in 21% to 38% of all cases, and the sole isolated bacteria in 40-75% of all positive cultures (Kelly et al, 2009, Pottinger et al, 2012). Other studies looking specifically at open procedures have found *P. Acnes* contamination in 10% of all taken swabs, representing 83% of all positive cultures (Mook et al, 2015)

*P. acnes* is a gram-positive, non-spore forming anaerobic bacillus found in the pilosebaceous follicles of the skin as well as upper respiratory and digestive mucosae (Hudek et al, 2014). Because of the larger number of hair follicles and sebaceous glands found in the chest, axilla and back there is an increased presence of P. acnes in the normal flora of these regions (Hudek et al, 2014). It is difficult to diagnose clinically and laboratory techniques require prolonged and specialised cultures (Lavergne et al, 2017). Superficial skin colonisation is high, reported in as many as 73% of patients undergoing TSA (Koh et al, 2016). Furthermore positive deep cultures have been found in approximately 30-42% undergoing primary total shoulder arthroplasty (Levy et al., 2013/Matsen et al., 2015). The present hypothesis is that the shoulder joint is inoculated with P. Acnes from contamination of the deep dermal layer that is unable to be adequately sterilized by standard preparations and prophylactic antibiotics (Chuang et al, 2015/Dizay et al, 2017).

The current method to reduce post op *P. acnes* infections is to use topical skin preparations as well as prophylactic antibiotics during surgery. However, the standard surgical prophylaxis does not seem to decrease the bacterial load, most likely because it does not penetrate the dermal layer (Saltzman et al, 2009/Dizay et al, 2017).

Patel et al. (JSES, 2009) analysed a prospective cohort of patients comparing the colonization of various body sites looking specifically at *P. Acnes*. Superficial skin swabs were taken from 3 separate sites around the shoulder as well as the anterior thigh and knee. *P. Acnes* was most prevalent on the skin at the anterior and posterior acromion sites of the shoulder and men involved in the study had a much higher prevalence of *P. Acnes* than their female counterparts.

Further work by Chuang et al (2015) in a prospective study of 51 patients undergoing shoulder arthroscopy showed *P. Acnes* colonization at portal sites in 72.5% of patients prior to skin preparation and further deep culture inoculation following preparation in 19.6% of patients. Notably all patients who had positive deep cultures also showed positive skin colonization.

Saltzman et al. (*JBJSAm,* 2009) evaluated the efficacy of three different surgical skin-preparation solutions on the eradication of bacteria from the shoulder during both arthroscopic and open procedures. A total of 150 patients had their shoulders prepared with ChloraPrep (2% chlorhexidine 70% isopropyl alcohol), DuraPrep (0.7% iodophor and 74% isopropyl alcohol) or Povidone-Iodine (0.75% iodine +1% iodine paint) prior to their shoulder procedure. Swabs were taken following skin prep and cultured for 7 days. Overall the ChloraPrep group had the lowest rate of positive cultures with 7%. This was found to be superior to both the Povidone-Iodine and DuraPrep groups in overall bactericidal activity. As a subgroup *P. Acnes* continued to have a positive culture rate of 15% in the Povidone-Iodine group, 12% in the DuraPrep group and 7% in the ChloraPrep group none of which were found to be statistically significant differences.

In 2014 Lee et al (*JBJS)* evaluated the efficacy of superficial ChloraPrep in eradication of *P. Acnes* from deep dermal tissue. Following standard preparation with ChloraPrep (2% chlorhexidine, 70% isopropyl alcohol) with no systemic prophylactic antibiotics 2 separate 3mm punch biopsies were taken from subjects upper back and sent for culture. Seven of the ten (70%) subjects returned positive cultures for P. Acnes despite adequate skin preparation of which 4 subjects (40%) had both specimens culture positive.

Falconer et al (2016) in a prospective study of 40 patients attempted to determine the level of contamination from *P. Acnes* through 5 swabs taken during the procedure. Despite adequate skin preparation as well as the use of prophylactic antibiotics, thirteen patients (33%) had at least 1 positive culture for *P. Acnes.* Furthermore of significant importance was that 12 of the 31 positive swabs (39%) for *P.Acnes* came from the subdermal layer of the skin. From this it was concluded that the subdermal layer appeared to be the probable source of inoculation during arthroplasty.

Phadnis et al. (2016) examined the frequency of P. acnes isolation despite skin prep and prophylactic antibiotics. In their prospective study of 50 patients a combination of prophylactic IV cefazolin (2g) was given 30 min prior to skin incision and then the skin was prepared with ChloraPrep and allowed to dry. Pre-preparation, post-preperation, a dermal swab (swab taken after skin was incised from exposed dermal surface) and a dermal biopsy were then taken during the procedure. A total of 21 patients (42%) had positive pre-prep cultures thatdecreased to 6 patients (12%) having post-prep cultures. However, the dermal swab and biopsy had much higher positive culture rates with 53% and 38% respectively. This further suggested that despite adequate preparation and prophylactic antibiotics *P. Acnes*  remained a viable contaminant in the dermis.

In an attempt to further decrease contamination related to *P. Acnes,* Sabetta et al (JSES, 2015) completed a prospective study looking at the efficacy of benzoyl peroxide (BPO) in use in shoulder surgery. BPO has long been used in the dermatologic treatment of acne vulgaris of which is *P. Acne*s is thought to be the primary pathogen (McKeage and Keating, 2008). Its exact mechanism of action is unknown but it is thought to involve the interaction of its oxidised intermediates with various constituents of bacterial cells (McKeage and Keating, 2008).

This study by Sabetta (2015), involving 50 patients undergoing arthroscopic shoulder surgery had patients apply benzoyl peroxide 5% (BPO) topically to the surgical shoulder a total of 5 times before surgery. Pre-preparation swabs were taken from the both the operative arm and non-operative arm. The operative arm was then re-swabbed post prep with ChloroPrep. Aspirates of the glenohumeral joint post trochar placement along with 3 deep tissue samples were taken to determine the level of deep tissue inoculation. Two additional skin swabs that were taken prior to skin closure. It was found that BPO significantly reduced the number of superficial P. Acnes swabs from both the anterior and axillary swabs pre-prep compared to the non-operative arm that was not treated. No significant difference was noted on any of the deep tissue or post-prep swabs between groups. No clinical infections were noted at 9 months follow-up

Specifically looking at dermatological evidence of BPO and other skin treatments in the treatment of acne, meta-analysis has suggested that the combination of BPO with topical clindamycin superior to BPO products alone (Seidler et al, 2009).

Dizay et al. (JSES, 2017) analysed the use of topical BPO (5%) with clindamycin (1.2%) in its ability to eradicate P. Acnes from both superficial and deep tissue specimens of 65 patients undergoing various arthroscopic shoulder procedures. Patients were randomized into groups of application (1-10 days) prior to procedure with swabs being taken from 3 sites pre-op, post-BPO/C prior to prep and a third deep tissue swab from the arthroscopy portal post procedure. Superficial colonization was eliminated in 23 of 31 (74.2%) patients who had positive P. Acnes cultures. The efficacy of eradication appeared to improve with the number of applications with 78.9% of patients having negative swabs with >1 application of BPO/C. Deep cultures were positive in 3.1% of patients overall with none being reported from the >1 application group. No clinical infections occurred over follow-up and only 1 reported skin reaction was recorded as a side effect of the BPO/C treatment.

STUDY HYPOTHESIS

**Primary Hypothesis**

Topical benzoyl peroxide (5%) with clindamycin (1%) is of equal or greater effectiveness compared to benzoyl peroxide (5%) and pHisohex (1% triclosan, sodium benzoate 5mg/mL benzyl alcohol 5mg/mL) wash in eradication of *P. Acnes* contamination in primary total shoulder arthroplasty.

**AIMS**

**Primary Aims**:

1. To determine the efficacy of 3 separate topical skin preparations in reducing contamination by *P. Acnes* in primary total shoulder arthroplasty.

**Secondary Aims**:

1. To determine the level of contamination, inoculation and clinical manifestations of infection with *P. Acnes* in primary total shoulder arthroplasty.
2. To determine the level of compliance relating to application of 3 different shoulder preparations prior to arthroplasty.
3. To determine risk factors related to *P. Acnes* contamination in total shoulder arthroplasty
4. To compare levels of contamination with *P. Acnes* between total shoulder arthroplasty and total knee arthroplasty using 3 different topical skin preparations (separate arm of study which may be completed at a later date)

STUDY DESIGN

The study will be a prospective randomized control trial with 3 arms. Recruitment will be via eligible candidates who provide consent to partake in the study. Patients will be offered to partake in the study from practices and surgeons who plan to undertake total shoulder arthroplasty in those patients.

Patients included in the study will be between the ages 30 to 90 years of age undergoing primary total shoulder arthroplasty. Primary arthroplasty will include both anatomic and reverse total shoulder arthroplasty. Both male and females will be included in data collection. Those undergoing arthroplasty in the treatment of fracture or rotator cuff tears will also be included.

Excluded patients will be those who chose not to provide or are unable to provide consent for the study. Patients who have had previous shoulder arthroplasty or other surgical procedures within the previous 6 months (open and arthroscopic) on the operative side will also be ineligible for participation. Those with active infection, allergy to product or pregnant will be excluded. Patients who have had any form of injection into the shoulder in the previous 6 months will also be excluded.

Following recruitment, and informed consent an initial skin swab will be taken in the rooms of participating surgeons. Patients will then be allocated into 1 of 3 randomized groups of skin preparation prior to their procedure. Group 1 will wash with standard pHisohex wash (1% triclosan, sodium benzoate 5mg/mL benzyl alcohol 5mg/mL) the 2 days before (day and night) as well as the day of procedure (5 applications total). Group 2 will be asked to apply benzoyl peroxide 5% gel to the operative shoulder 2 days before (day and night) as well as the day of the operation (5 times total). Group 3 will be asked to apply combination benzoyl peroxide 5% with clindamycin gel 2 days (day and night) as well as on the day of procedure (5 applications total).

Surgical technique will be standardized across centres and surgeons. (see below)

Swabs will be collected and transported to Sullivan and Nicholaides where microbiological testing will take place.

Cultures will be kept for a total of 14 days.

Patients will be followed up clinically as per the Principle Investigating surgeon’s preference. Complications including infection will be collected. Those with suspected clinical infection will be treated accordingly as per recommended guidelines and surgeon decision.

*Table 1. Surgical groups*

|  |  |
| --- | --- |
|  | Surgical Groups |
|  | Group 1 | Group 2 | Group 3 |
|  | PHisohex group | BPO group | BPO/Clindamycin group |
| Sample size (n) | 35 | 35 | 35 |

Participant recruitment will commence in December 2017 and will require 1-2 years to reach a sample size with the desired statistical power. It is therefore anticipated that the entire study will be completed within 2 years.

METHODS

Setting

The Mater Hospital – Townsville

Population

***Selection Criteria***

*Inclusion Criteria:*

Patients scheduled to undergo primary shoulder arthroplasty (both anatomical and reverse total shoulder arthroplasty)

Male and female

Age 30-90

Able to provide informed consent

*Exclusion Criteria:*

Patients unable to comply with assessment requirements

Patients with active infection

Patients with BMI >40, (may impact on study)

Patients who are pregnant or planning on becoming pregnant during the course of the study

Patients unable to provide informed consent

Patients who have undergone previous arthroplasty, have had previous infection, previous surgical procedures or injection into the shoulder within the previous 6 months prior to surgery.

Patients with documented allergy to any of the skin preparation solutions

Recruitment

Potential participants who meet the selection criteria will be approached in clinic by the investigating surgeon and provided information on the study, with an opportunity to ask questions. Willing participants will be asked to provide consent for participation.

Consent

Each investigator will provide information to the patient of the purpose of the study and what their participation would involve in terms of the type and frequency of assessments throughout the study. The investigators will discuss foreseeable risks involved and potential benefits arising from the completing the study. Each potential participant will be provided an information sheet and invited to discuss taking part in the study with others. Patients will be informed by the investigator that they are free to refuse participation in the study, or to withdraw from the study at any time, without compromising their medical care. Patients will be informed that confidentiality of personal data will be maintained at all times and access to this information will be restricted to authorised personnel only.

All participants shall provide consent prior to participation in study-specific preoperative assessments. Participants will also be required to consent for investigators to electronically capture and store information on the Amplitude online platform for current and future use in ORIQL research, following HREC approval. Any data provided to the sponsor will be de-identified.

Randomisation and blinding

Randomization will be performed at the time of patient consent and during the initial consult at the investigators’ clinic. After patient enrolment onto the Amplitude online platform, the practice nurse will notify the ORIQL Research Coordinator, who will assign the patient to a study group based on a predetermined list of random numbers using a random number generator. The Research Coordinator will then promptly notify the practice nurse of the surgical group the patient will be assigned to.

Applicants will not be blinded as to which treatment they receive as this is unlikely to affect outcomes of the study and is equally challenging as products are labelled in commercial bottles.

Time Points

*Table 2. Schedule for study outcome assessment*

|  |  |
| --- | --- |
| **Assessments** | **Study Visits** |
| Pre-Op | Surgery | Postoperative |
| 2 weeks | 6 weeks | 3 months | 6 months | 12 months |
| **Informed consent** | ✓ |  |  |  |  |  |  |
| **Orthopaedic evaluation** | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Informed consent** | ✓ |  |  |  |  |  |
| **Pre-prep swab** | ✓ |  |  |  |  |  |
| **Intraoperative swabs (x4)** |  | ✓ |  |  |  |  |  |
| **Compliance survey** |  |  | ✓ |  |  |  |  |

Patient Information and Demographic Data

Patient demographic data (age, gender, BMI), medical history and concomitant medication information and will be gathered preoperatively and input directly into the Amplitude clinical outcomes database. Patients will answer PROMS assessment questionnaires directly into the Amplitude clinical outcomes platform. Only the patient, the patients surgeon, the practice nurse and the Research Co-ordinator have access to the patient’s identified data. Data sets for this study will be used and retained in a re-identifiable form.

Study Outcomes

* Contamination and inoculation with *P. Acnes* will be determined via microbiological analysis. Positive cultures will be noted and compared statistically between groups. From this data efficacy between preparations can be determined.
* Compliance with the various skin preparations will be completed at the 2 week follow-up via survey.

Surgical Procedure

Surgical technique will be standardized across centres and surgeons. All patients will undergo general anaesthetic with or without block dependent on anaesthetic preference and patient suitability. Patients will be placed in beachchair positioning for the procedure.

Following application of 1 of the 3 preparations prior to surgery all patients will have their shoulder prepped with Chloroprep (2% chorhexidine gluconate and 70% isopropyl alcohol). Prophylactic antibiotics (Cephazolin 30mg/kg up to2g Intravenously) will be given to all patients as standard practice. Those with impaired renal function will be given an appropriate renally adjusted dose. Those with a cephalosporin allergy will be given Vancomycin 15mg/kg IV. Standard draping of the arm combined with application of a sticking barrier (Opsite/Ioban) will be applied to the entire operative site. Following prepping and draping surgeons will change their outer gloves to limit potential contamination of the surgical field. A deltopectoral approach will be used for all arthroplasties.

Swabs will be taken on the day of procedure as follows:

1. Prior to surgical skin preparation in theatre
2. Dermis post skin incision
3. Upon entry into the glenohumeral joint
4. Skin swab on closure

A single swab will opened and left in theatre on the main scrub table to act as a control.

Following skin incision the scalpel blade used will be discarded to avoid potential contamination of deep tissues. Prosthesis used will be dependent on surgeon preference and patient suitability. Wound closure techniques and materials as well as post-operative dressings will be as per surgeon preference.

Surgical Data

Standard intraoperative data currently recorded by the investigating surgeons will be captured (Appendix 4: Intraoperative Data Collection Form\_THA) and includes:

* Date of surgery
* Operated joint/site
* Surgeon
* Surgical approach
* Anaesthesia class and type
* Estimated blood loss
* Intraoperative complications
* Prosthesis implanted (model & serial numbers), if relevant
* Concomitant medication
* Adverse event
* Device deficiencies

Power calculation

Assuming Type I error (alpha) to 5% (p = 0.05) and Type II error (beta) to 0.2 (power equal to 80%), the sample size calculated to be able to observe [what you’re looking at] was 35 participants per study group; a total of 105 study participants. We will therefore require a total of 105 patients for completion of this study.

Statistical analysis

The null hypothesis of this study is “Topical benzoyl peroxide (5%) with clindamycin (1%) is of equal or lesser effectiveness compared to benzoyl peroxide (5%) and pHisohex (1% triclosan, sodium benzoate 5mg/mL benzyl alcohol 5mg/mL) wash in eradication of P. Acnes contamination in total shoulder arthroplasty”. All data will be analysed using the Statistical Sciences (SPSS, Version 22).

DATA MANAGEMENT

Data will be captured using Amplitude Clinical Outcomes (Amplitude), a web-based patient management system that is currently used by ORIQL for multi-site clinical data management for all hip, shoulder and knee arthroscopy patients of the orthopaedic surgeons affiliated with ORIQL. Patients will be enrolled into Amplitude at the time of booking their date of surgery, irrespective of participation in this trial. The Participant information sheet pertaining to the study is available within the Amplitude platform and will be accessible (or provided in hardcopy, if preferred) to new patients after initial discussion of the study with the Investigating surgeons.

Patients consent to trial will be captured using Amplitude and all participant information regarding the trial is provided within the platform. The database is password protected, and stored on secure servers. The Amplitude system has been accredited for Level 3 compliance by the HSCIC (Health & Social Care Information Centre) in the UK, the highest level of security compliance. Each surgeon and their care team is only able to access data for their specific patients. The ORIQL Research Coordinator is the only person who is able to access identifiable study patient data from all participating surgeons for a given study. The Research Coordinator will be responsible for collating and de-identifying combined patient data from both surgeons in the current study for analysis. Analysis will be performed on de-identified data.

Data generated in the course of the study, including the final report and scientific literature, will be retained for a period of 15 years.

Data collected by Investigators, including mandatory patient demographic data, will be input directly onto the ORIQL/Amplitude database by the patient and the care team.

ETHICAL CONSIDERATIONS

This study will be submitted to the Principal Investigators’ Institutional Human Research and Ethics Committees: [insert relevant HREC here]. Recruitment for the study will not commence prior to obtaining written HREC approval. The study will be registered prior to trial commencement with the ANZCTR.

The study will be managed and monitored by the Sponsor’s Clinical Research Department. The ORIQL Clinical Research Coordinator will act as the contact between the study site and sponsor to ensure quality conducted of the study. Throughout the study the ORIQL Research Coordinator will maintain written and oral communication with the investigators and their care team regarding the ongoing compliance of the study. All monitoring and project management will be performed in accordance with ICH GCP and ISO 14155.

No adverse events or complications are anticipated as a result of the study. Should any unanticipated adverse device effects occur, the Research Coordinator will ensure these are documented by the Investigator and reported to the HREC as soon as possible.

FEASIBILITY

The administrating institution has conducted multiple research projects on patients undergoing surgery. Approximately 150 shoulder arthroplasties are performed by the investigating surgeons between the study sites annually. Therefore, we do not anticipate any problems in achieving the desired sample size for this study over a 2 year period.

DISSEMINATION OF RESULTS AND PUBLICATION

The results of the study will be presented at national and international orthopaedic scientific meetings such as the Australian Orthopaedic Association (AOA) Annual Scientific Meeting. Results will be published in a high impact surgical journal and will be disseminated via various forms of media. Authorship will be under the name of Investigators from ORIQL contributing to this research project.

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