Protocol

“A prospective single-blind placebo-controlled trial to establish the efficacy and tolerability of 10% Povidone-Iodine for nasal *S. aureus* and MRSA decolonization among patients undergoing same-day surgery”.

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INTERVENTIONAL
RESEARCH PROTOCOL TEMPLATE
(HRP-503a)

STUDY INFORMATION

- **Title of Project:**

A prospective single placebo-controlled trial to establish the efficacy and tolerability of 10% Povidone-Iodine for nasal *S. aureus* and MRSA decolonization among patients undergoing same-day surgery

- **Principal Investigator Name**

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1.0 Research Design

1.1 Purpose/Specific Aims

To evaluate the efficacy and tolerability of 10% povidone-iodine in eliminating nasal carriage of *S. aureus* and MRSA.

A. Objectives

To determine whether a more convenient, single-dose, pre-operative 10% povidone-iodine (PI) application is effective in reducing nasal carriage of *S. aureus* and MRSA.

B. Hypotheses / Research Question(s)

We expect a statistically significant decrease in *S.* aureus/MRSA colonization in nasal cultures taken perioperatively after intervention in patients who received pretreatment with PI as compared to patients who received sterile saline.

1.2 Research Significance

According to some estimates, as many as 25%-30% of healthy individuals in the community have nares colonized with *S. aureus*, while 1%-2.6% have MRSA-colonized nares[1]. This nasal carriage of *S. aureus* and MRSA is a known risk factor for post-operative wound infections in several different types of surgery[2]. Many, if not most infections due to *S. aureus* occur in colonized persons[1]. In implant-based breast reconstruction surgeries for instance, nasal carriers of *S. aureus* are 3 to 6 times more likely than noncarriers to develop nosocomial infections with this pathogen[3]. Similarly, studies have revealed that MRSA nasal colonization may be an independent risk factor for surgical site infection[4]. In a particular study, the MRSA PCR-positive group had a 9-fold increased risk of MRSA surgical site infection compared to the MRSA PCR-negative group, though the former had a low incidence at 1.86%[4]. Coagulase-negative staphylococci (CoNS) are also important etiological agents of post-operative infection[5, 6]. Together, *S. aureus* and CoNS (predominantly *S. epidermidis*, a common denizen of human skin that can colonize nares as well) account for 50-60% of prosthetic joint infections in roughly equal proportions[5, 6].

The agent typically used in assessing the effectiveness of nasal decolonization is mupirocin, which has been shown in some studies to eradicate colonization in up to 92% of post-operative nasal cultures[7]. Randomized controlled trials comparing nasal mupirocin with placebo in general, gynecologic, neurologic, orthopedic, and cardiothoracic procedures have demonstrated that mupirocin reduces the rate of surgical-site infection among known carriers of *S. aureus*[2]. In fact, the American Society of Health-System Pharmacists recommends screening and nasal mupirocin decolonization for *S. aureus*-colonized patients before total joint replacement and cardiac procedures[8]. Likewise, some studies indicate that nasal mupirocin can decolonize CoNS, with only 1.3% of CoNS isolated from the nares of orthopedic surgery patients and 1.6% of samples from prosthetic joint infections displaying some resistance to mupirocin[5].

The mupirocin protocol for nasal decolonization discussed in the literature entails nasal application of mupirocin twice a day for 5 days before surgery[7]. Our end goal is to determine whether a more convenient, single-dose, pre-operative 10% povidone-iodine (PI) application can offer similar if not better surgical site infection results as mupirocin. The first step towards this goal is to evaluate the efficacy and tolerability of 10% povidone-iodine in eliminating nasal carriage of *S. aureus* and MRSA.

1.3 Research Design and Methods

Implement povidone-iodine (10%) pre-operative nasal decolonization for patients undergoing same-day surgery and evaluate efficacy and tolerability of this intervention in eradicating nasal colonization.

A. **Research Procedures**

This will be a prospective single-blinded randomized placebo-controlled trial of two applications of a nasal 10% PI solution used on the intranasal mucosal surfaces of each nostril in the preoperative holding area within 2 hours prior to surgical incision compared with sterile saline using the same technique. Both the PI and sterile saline will be applied by rotating the swab over the intranasal mucosal surface for 15 seconds; this process will be performed twice for both nostrils, using a new swab for each of the 4 applications. 200 subjects will be chosen from a pool of patients arriving at University Hospital, Newark, NJ for outpatient surgery. Inclusion criteria include community-based patients ages 18-80, ASA 1-3 who will be undergoing an outpatient surgery scheduled for at least 1 hour and up to 6 hours duration. Exclusion criteria include pregnancy, allergy to povidone-iodine, infectious indication for surgery or preexisting known infection/wound, known immunocompromised state, use of antibiotics, chemotherapy, or steroids within 1 month prior to surgery. Additionally, patients presenting for surgeries where field avoidance prevents intraoperative access to the nares (e.g., ENT/OMFS/ophthalmology procedures) will be excluded. Patients will be randomly divided into two groups: control (sterile saline) vs. experimental (PI) This will be done via simple randomization using a computer program that assigns patients as they present into either the control or experimental group while maintaining an overall approximately even ratio of subjects in each group.

B. Data Points

Potential subjects will be identified from surgical schedule. Patients will be asked for informed consent in the same-day surgery (SDS) unit. They will be given sufficient time to read the IC document and ask questions. While in the preoperative holding area, patients will be asked to sit upright at a 45-90° angle to prevent drainage into the nasopharynx. All patients will first be swabbed for a nasal swab specimen, once in each nostril. Patients will then receive the appropriate nasal applications depending on the group into which they were sorted: Povidone-Iodine or saline. The tolerability assessment of investigating drug will be done with every subject at the Pre-operating room and PACU by a few criteria as burning/itching, pain, irritation, epistaxis, runny nose, and others. Nasal swab specimen will be obtained by the anesthesiologist intraoperatively 1, 2 and 3 hours after investigational drug application as studies have shown that there a significant decrease in colony-forming units of MRSA even within 1-hour post-treatment [9, 10]. These cultures may be intraoperative or postoperative depending on the length of surgery. There will also be a nasal swab specimen obtained while the patient is in the PACU. Study subjects will be stratified according to age, sex, comorbidities, and ethnicity. Additionally, the type of surgery, duration of surgery (Incision start to incision close), number of surgeons present during the procedure (Include all individuals scrubbed in), postoperative hospital stay length, and intraoperative time (patient in OR to patient out OR) will be used in data analysis. The purpose is to identify variables that increase the incidence of surgical site infection.

C. Study Duration

The study will take approximately 2 years, but chart review may continue up to 4 months after the last patient in the study has their procedure. Chart review of subject's postoperative surgical clinic visits will be performed up to 30 days to monitor for any surgical site infection.

D. Endpoints

The primary study end point is the decrease in S. aureus/MRSA colony forming units (CFU) in nasal swab specimen taken perioperatively after intervention in patients who presented with a positive pre-interventional nasal swab specimen. A secondary endpoint is the presence or absence of surgical site infections at 7 and up to 30-day postop intervals (per retrospective chart review). The review includes an assessment of post-operative infections, complications, and prescribing antibiotics (name, dose, number of days, completing).

1.4 Preliminary Data

N/A

1.5 Sample Size Justification

We assumed that *S.* aureus/MRSA suppression in 20% of patients would be clinically relevant and that up to 5% of patients may have suppression even without treatment. Using a one-sided alpha of 0.05 and a beta of 80%, we calculated that we would need at least 85 patients in each group for a total of at least 170 patients. A paired t-test will be used to compare preintervention nasal culture CFUs to 1- hour post application, 2- hour post application, and 3-hour post application, nasal culture CFUs. A 2-sample t test will be used to compare the difference in pre- and post- intervention CFUs between the control and experimental groups at any endpoint. Additionally, mixed regression analysis will be used to determine the effect of the intervention on the CFU counts over all follow-up time points.

1.6 Study Variables

A. Independent Variables, Interventions, or Predictor Variables

Independent variable will be whether the patient received a nasal swab with Povidone-Iodine or sterile saline.

B. Dependent Variables or Outcome Measures

The decrease in CFUs in multiple time spans after intervention.

1.7 Drugs/Devices/Biologics

A. Schedule and Administration

Povidone-Iodine 10% solution will be given intranasally as a swab with two swabs/nostril for patients in the experimental arm of the study. The control arm will be given sterile saline via the same method.

B. Drug/Device Accountability and Storage Methods

The study drugs will be dispensed by the pharmacy. The study drugs will be administered by study investigators.

1.8 Specimen Collection

A. Primary Specimen Collection

- **Types of Specimens**: 4 sets of nasal mucosal samples per subject to be collected ~~by~~ a investigator at preoperative, intraoperative, and postoperative intervals. A study participant number will be associated with each sample.
- **Transport**: All cultures will be sent to an outside lab for testing per the following protocol. All swabs will be placed in a 15 mL conical screw-top tubes containing sterile Phosphate Buffered Saline (PBS) solution. The samples will then be shipped the same day by 3 PM in a foam-insulated cooler with ice packs via overnight delivery to the testing facility.
- **Processing**: Swabs will be analyzed and enumerated by an outside testing facility for the presence of *S. aureus*, MRSA, and *S. epidermidis*.
- **Storage**: The specimens will be stored in the cooler described above and will be shipped out to the lab that same day. Prior to shipping, they will only be accessed by the study team.
- **Disposition**: Samples will be discarded after the lab has analyzed them.

B. Secondary Specimen Collection

- N/A

1.9 Data Collection

A. **Primary Data Collection**

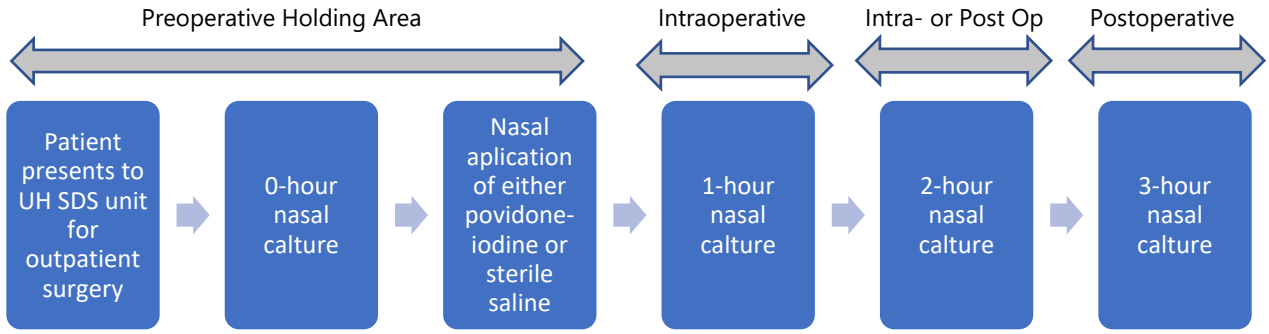
- **Location**: Data collection will occur in the preoperative holding area, operating rooms, and post-anesthesia care unit of the University Hospital, Newark, NJ.
- **Process of Data Collection**: The investigator who is applying the saline or 10% PI to the study subjects will not be blinded. Nasal cultures will be obtained by the study team members. Dr. Dennis Grech will be overseeing the entire study.
- **Timing and Frequency**: There will be swab collections prior to the procedure, at the one-, two-, and three-hour marks after saline or 10% PI is administered.
- **Procedures for Audio/Visual Recording**: N/A
- **Study Instruments**: n/a
- **Ethnographic Studies, Interviews, Or Observation**: N/A
- **Subject Identifiers**: MRN only

B. **Secondary Data Collection**

- N/A

1.10 Timetable/Schedule of Events

Figure 1 Timeline of study protocol



The study will last approximately 2 years from the beginning.

2.0 Project Management

2.1 Research Staff and Qualifications

Dr. Dennis Grech will be available all days of the study. Having worked in this hospital for many years, he is very knowledgeable about the study site, the culture, and the patient population. He will be enlisting the help of study assistants to aid in the collection of data and application of the nasal swabs but will be directly overseeing all of this to ensure everything is in order.

2.2 Research Staff Training

All involved study team members will be trained how to perform data collection and nasal swab application correctly.

2.3 Other Resources

N/a

2.4 Research Sites

Rutgers – New Jersey Medical School; University Hospital, Newark, NJ.

3.0 Multi-Center Research

N/A

4.0 Subject Considerations

4.1 Subject Selection and Enrollment Considerations

A. Method to Identify Potential Subjects

Subjects will be chosen from a pool of patients arriving at University Hospital, Newark, NJ for outpatient surgery.

B. Recruitment Details

Subjects meeting the inclusion criteria will be identified by the anesthesiologist preoperatively and be given information about the study and what their participation entails. They will also be given a recruitment flyer with information and will have the opportunity to ask any questions they may have.

C. Subject Screening

- **Inclusion Criteria**

- community-based English or Spanish speaking patients ages 18-80
- willing and able to consent
- American Society of Anesthesiology (ASA) 1-3
- undergoing an outpatient surgery for at least 1 hour and up to 6 hours duration

- **Exclusion Criteria:**

- pregnancy
- allergy to povidone-iodine
- infectious indication for surgery or preexisting known infection/wound
- immunocompromised state
- use of chemotherapy or steroids within 30 days prior to surgery
- use of antimicrobial therapy within 30 days prior to surgery
- surgeries where field avoidance prevents intraoperative access to the nares

D. Privacy Protections

No information about the patients will be revealed to anyone except the study team and providers involved in the care of the patients.

4.2 Obtaining Identifiable Information About Non-Subjects

N/A

4.3 Number of Subjects

A. Total Number of Subjects

Using a one-sided alpha of 0.05 and a beta of 80%, we calculated that we would need at least 85 patients in each group for a total of at least 170 patients.

B. Total Number of Subjects If Multicenter Study

N/A

C. Feasibility

Based on the volume of same-day surgical procedures at University Hospital, Newark, NJ and the wide inclusion criteria for this study, having 170 total patients for the study should be feasible.

4.4 Consent Procedures

A. Consent Process

- **Location of Consent Process**
  In the SDS unit of University Hospital.
- **Ongoing Consent**
  N/A
- **Individual Roles for Researchers Involved in Consent**
  The study team members will be obtaining the nasal swabs and will be informing the patient of the study and obtaining consent.
- **Consent Discussion Duration**
  Enough time will be spent discussing the study with the patient until all patient's questions and concerns have been addressed.
- **Coercion or Undue Influence**
  Patients will be told that they are not obligated to participate in the study and that their care will not be affected by their decision.
- **Subject Understanding**
  Key questions will be asked of the patient during the discussion to verify the patient's understanding of the study and their role within it.
- **Protecting Privacy**
  Only the patient and patient's guest in the SDS unit will be present during the discussion.

B. Waiver or Alteration of Consent Process

- **Waiver or Alteration Details**
  N/A
- **Destruction of Identifiers**
  N/A
- **Use of Deception/Concealment**
  N/A

C. Documentation of Consent

- **Documenting Consent**
  Individuals will be asked to sign the consent document.
- **Waiver of Documentation of Consent (i.e., will not obtain subject's signature)**
  N/A

4.5 Special Consent Populations

A. Enrolling Minors-Subjects Who Are Not Yet Adults

- **Parental Permission**
  N/A
- **Non-Parental Permission**
  N/A
- **Assent Process**

N/A

- **Documentation of Assent**
  N/A
- **Reaching Age of Majority During Study**
  N/A

B. Enrolling Wards of the State
N/A

- **Research Outside of NJ Involving Minors**
  N/A

C. Enrolling Non-English-Speaking Subjects
Spanish speakers will be enrolled. The Spanish version of the Informed Consent Form will be provided for Spanish speakers. **Process for Non-English-Speaking Subjects**.
The study team will use the Language Line Translator service the University Hospital provides for Spanish-speaking study participants.

- **Short Form Consent for Non-English Speakers**
  N/A

D. Enrolling Adults Lacking Decision-Making Capacity (Surrogate Consent)
N/A

- **Assessing Adult Capacity to Consent**
  N/A
- **Selecting a Surrogate & Consent Process**
  N/A
- **Subject Assent**
  N/A
- **Selecting a Witness to the Surrogate Consent Process**
  N/A
- **Removing a Subject**
  Any patient who wishes to be removed from the study will be removed immediately. Completion of the study regimen is defined as 2 applications of sterile saline or PI preoperatively and at least one intraoperative culture obtained perioperatively after surgical incision.

E. Special Consent Considerations
N/A

4.6 Economic Burden and/or Compensation for Subjects

A. Expenses
N/A
B. Compensation/Incentives
N/A
C. Compensation Documentation
N/A

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4.7 Risks of Harm/Potential for Benefits to Subjects

A. Description of Risks of Harm to Subjects

- **Reasonably Foreseeable Risks of Harm**
  Minimal risk of harm given only intervention is nasal swabs.

- **Risk of Harm from an Intervention on a Subject with an Existing Condition**
  N/A
- **Other Foreseeable Risks of Harm**
  N/A
- **Observation and Sensitive Information**
  N/A

B. Procedures which Risk Harm to Embryo, Fetus, and/or Pregnant Subjects
N/A

C. Risks of Harm to Non-Subjects
N/A

D. Assessment of Social Behavior Considerations
N/A.

E. Minimizing Risks of Harm

Care will be taken by the investigators to minimize any potential discomfort patients may feel from the nasal swabs. Electronic study subject data (demographic data, weight, height, medical history, diagnosis, surgery type, co-morbidities, concomitant medications, anesthesia/surgical record, surgical visit notes) will be obtained from the subjects' electronic medical record and stored on an excel file that is maintained on a password protected hard drive in a locked room in MSB E-546.

- **Certificate of Confidentiality**
  N/A
- **Provisions to Protect the Privacy Interests of Subjects**
  N/A

F. Potential Direct Benefits to Subjects

Patients in the experimental group may have a decreased risk of surgical site infection post-operatively.

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA)
N/A

5.2 Family Educational Rights and Privacy Act (FERPA)
N/A

5.3 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)
N/A

5.4 General Data Protection Regulation (GDPR)
N/A

5.5 NJ Access to Medical Research Act (Surrogate Consent)
N/A

6.0 Data Management Plan

6.1 Data Analysis
We expect a statistically significant decrease in S. aureus/MRSA colonization in cultures taken perioperatively after intervention in patients who received pretreatment with PI as compared to patients who received sterile saline. We assumed that S. aureus/MRSA suppression in 20% of patients would be clinically relevant and that up to 5% of patients may have suppression even without treatment. Using a one-sided alpha of 0.05 and a beta of 80%, we calculated that we would need at least 85 patients in each group for a total of at least 170 patients. A paired t-test will be used to compare preintervention

nasal culture CFUs to 1- hour postintervention, 2- hour postintervention, and 3-hour postintervention nasal culture CFUs. A 2-sample t test will be used to compare the difference in pre- and post-intervention CFUs between the control and experimental groups at any endpoint. Additionally, mixed regression analysis will be used to determine the effect of the intervention on the CFU counts over all follow-up time points.

The data will be stratified by type of surgery, duration of surgery, and number of surgeons present throughout the procedure. Additionally, the variables age, sex, race, comorbidities, postoperative hospital stay length, and intraoperative time will be used in data analysis. In addition, postoperative surgical site infection (SSI) surveillance for the study participants will be conducted at 7 and 30-day postop intervals.

An intent to treat analysis will include those who are enrolled in the study and meet eligibility requirements for the study. A per protocol analysis will include all eligible patients who complete the assigned study regimen. Completion of the study regimen is defined as 2 applications of sterile saline or PI preoperatively and at least two cultures obtained perioperatively.

6.2 Data Security

Clinical data for participants will be stored in REDCap. REDCap is a secure, web-based application. The server is located at Rutgers University and data is stored on secure networks behind a managed firewall. Data abstractors and clinical investigators will be the only ones who access to identified dataset. Other study members will only have access to data in aggregate or de-identified datasets. Signed IC will be kept inside the locked cabinet

6.3 Data and Safety Monitoring

[This section **is required** when research poses greater than minimal risk of harm to subjects.]

A. Data/Safety Monitoring Plan

N/A

B. Data/Safety Monitoring Board Details

N/A

6.4 Reporting Results

A. Individual Subjects' Results

Chart review of the electronic medical record will be used to follow up on patients' visits with their surgeons to determine presence or absence of surgical site infections at 7 and 30-day post-operative intervals.

B. Aggregate Results

Research results will not be shared with patients personally.

C. Professional Reporting

Results from the study will be written into a manuscript for submission into an academic journal and possibly presented at an appropriate medical conference to share results with the scientific community.

D. Clinical Trials Registration, Results Reporting and Consent Posting

A description of this clinical study will be available on ClinicalTrials.gov, as required by U.S. law.

6.5 Secondary Use of the Data

N/A

7.0 Research Repositories – Specimens and/or Data

N/A

8.0 Approvals/Authorizations

Uploaded

9.0 Bibliography

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