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Title: Post-Mastectomy Surgical Pocket Irrigation with Triple Antibiotic Solution vs Chlorhexidine Gluconate: A Randomized Controlled Trial Assessing Surgical Site Infections in Immediate Tissue Expander Breast Reconstruction

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1.0 Background

Breast reconstruction with tissue expander (TE) remains widely performed technique of breast restoration after mastectomy.[1] During first stage of reconstruction breast TE is placed at mastectomy site. Most commonly TE is placed into surgically created pocket below the pectoralis major and serratus muscles in the mastectomy wound (Figure 1). Alternatively, TE can be placed into subpectoral muscular pocket created with additional placement of acellular dermal matrix (ADM) sling (Figure 2). Regardless of surgical method of placement, TE is expanded gradually postoperatively over a period of several weeks until the desired size is achieved. Both techniques demonstrate comparable postoperative results including similar postoperative surgical site and tissue expander infection rates. [2]

The incidence of postoperative wound infection including TE infection after breast reconstruction ranges between 5-20% [2,3,4,6] Recently, several studies demonstrated that intra-operative irrigation of surgical pocket with antibiotics containing solution before insertion of breast TE resulted in a decrease of postoperative infection rate .[5,8,9] Irrigation of surgical wound with triple antibiotic solution (1 g of cefazolin, 50,000 U of bacitracin, and 80 mg of gentamicin in 500 mL of NS) was found to decrease bacterial growth associated with periprosthetic infections in both breast augmentation and reconstructive patients [5,10]. The Department of Plastic Surgery at Vanderbilt University routinely irrigates surgically created muscular pocket with triple antibiotics solution before placement breast TE. This decreased the postoperative infection rate within our department to 14%. Despite improvement in incidence of postoperative infection after application of triple antibiotic solution, some authors suggested that this technique has several drawbacks. For example, most antimicrobials agents are effective against microorganisms when drug exposure occurs during bacteria's logarithmic growth phase. Therefore, brief irrigation of surgical pocket with antibiotics does not provide sufficient contact time with bacteria in order to efficiently kill pathogenic microorganisms.

In order to further enhance antisepsis inside surgical pocket before placing breast TE we purpose to use 0.05% chlorhexidine (CHG) instead of triple antibiotic solution. Several recent studies demonstrated exceptional antiseptic properties of CHG derivatives. [8, 9,12-14] CHG is widely used for preparation of the surgical field and preoperative hand

scrubbing. It demonstrates broader bacterial coverage compared to povidone iodine based solutions. More recently several reports demonstrated that irrigation of chronically infected surgical wounds with 0.05% CHG decreases bacterial contamination without inhibiting wound healing or toxic side effects[8]. Exposure to a concentration of 0.05% CHG effectively produced a 5- to 6-log reduction in microbial recovery. Effective bacterial reduction was observed with both gram-positive and gram-negative surgical isolates. Specifically, antibacterial effect of CHG was prominent towards biofilm-forming strains associated with infection of prosthetic devices such as TE.[8]

We hypothesize that intraoperative irrigation of surgical pocket with 0.05% CHG solution before insertion of breast TE allows for more significant reduction of postoperative wound infection compared to similar irrigation with triple antibiotic solution in women undergoing bilateral TE-based breast reconstruction.

We intend to perform a prospective randomized study and compare the incidence of surgical wound infection between mastectomy wounds irrigated with triple antibiotic solution (one side) and 0.05% CHG (opposite side) in patients undergoing bilateral breast reconstruction.

1.0 Rationale and Specific Aims

Specific aim: to evaluate efficacy of 0.05% CHG solution to reduce postoperative surgical site infections compared to triple antibiotic solution in women undergoing breast reconstruction with TE.

2.0 Animal Studies and Previous Human Studies

Antimicrobial effects of 0.05% CHG were studied both *in vitro*, *in vivo* and on human subjects previously [8-14]. However, efficacy of this solution in decreasing incidence of surgical infection after breast reconstruction with TE has never been evaluated.

3.0 Inclusion/Exclusion Criteria

Inclusion criteria: 18-81 years old females undergoing bilateral mastectomy who are candidates for immediate breast reconstruction with TE (either total muscle coverage or ADM-based techniques).

Exclusion criteria: patients undergoing unilateral breast reconstruction, reconstruction with autologous tissue, bilateral reconstruction with other reconstructive techniques (autodermal flaps, *etc*) performed on either breast, patients allergic to one or more components of the antibiotic solution, patient allergic to CHG.

4.0 Enrollment/Randomization

Study population

The study is intended to be prospective randomized clinical trial.

Randomization

Site of application of CHG solution (either left or right surgical wound) in each patient will be randomly assigned by coin flipper application at random.org website (http://www.random.org/coins/). Triple antibiotic solution will be used on contralateral side and used as a control. Randomization will occur on the day of the operation.

Randomization of subjects will not be performed. Each patient will serve as self-control (contralateral surgical wound where triple antibiotic will be applied will be control side).

Blinding/Data Collection

Side of CHG application will be recorded by operating surgeon in patients database secured from other medical professionals participating in the study.

Examination of reconstructed breasts will be performed by experienced clinic nursing staff. The site of application of the CHG solution will not be disclosed during clinic visit to nursing staff. The collection of data will be provided by Marcia Spear, DNP, ACNP-BC without knowledge of the side of CHG application.

Clinical data associated with the patient will be extracted form StarPanel and entered in a RedCap database. Collected data will include: type of infection (major or minor), side of occurrence, route of antibiotic administration (iv or PO), length of hospitalization, any surgical treatment of infected area (incision and drainage, debridement, TE removal), the need for long term iv antibiotic therapy, pathogen based on culture results, days till recovery, type and time of repeat reconstruction.

5.0 Study Procedures

Breast reconstruction in each participating patient will be performed without deviation from standard technique routinely performed at Department of Plastic Surgery at Vanderbilt University. Upon completion of mastectomy, surgical pocket will be created either with pectoral and serratus muscles or with pectoral muscle and ADM. Before insertion of breast TE, randomly selected surgical pocket (either left or right) will be irrigated with 500ml of 0.05% CHG solution for 1 minute. After 1 minute CHG solution will be aspirated and TE inserted into surgical pocket following by muscle and skin closure. Accordingly, contralateral site will be irrigated with triple antibiotic solution for 1 minute, aspirated and breast TE will be inserted and wound closed in identical fashion.

Drugs that will be used:

-triple antibiotic solution: 1 g of cefazolin, 50,000 U of bacitracin, and 80 mg of gentamicin in 500 mL of NS. If the patient is allergic to either component – the allergen will not be used in the solution.

- 0.05% chlorhexidine solution –by diluting 6.25 ml of 4% chlorhexidine in 500ml of NS solution (1:80).

Outcome measures

Primary outcome:

- frequency of surgical site infection (as defined by CDC, http://www.cdc.gov/hai/ssi/ssi.html)

Surgical site infection will be subdivided into "minor" infection—defined by clinical signs of infection successfully treated with outpatient antibiotic therapy—or "major" infection requiring inpatient hospitalization for intravenous antibiotic treatment and/or any surgical treatment.

- frequency of TE infection (any infection of surgical site requiring surgical revision of TE)

6.0 Risks

We anticipate low risks given the previously demonstrated safety of CHG. Furthermore, minimal systemic absorption of CHG is expected since it will be used topically as irrigation. Allergic reaction to this drug including severe skin rash, swelling, trouble breathing and possibly death is rare.

7.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

The progress of the study will be discussed formerly at regularly scheduled research meetings. These will serve as a forum for the voicing of concerns or problems with the study. If participant safety is a concern, the research investigators will immediately notify the P.I. Adverse events will be reported to the IRB according to IRB policies and procedures, as there are specific guidelines at IRB Policy and Procedure III.L.1 that must be followed.

8.0 Study Withdrawal/Discontinuation

Patient can be taken out of the study if patient is allergic to CHG and if the study is closed.

9.0 Statistical Considerations

Sample size

The frequency of surgical site infection in patients undergoing breast reconstruction is 14 %.We anticipate a 4-fold reduction on infection rate with 0.05% CHG down to approximately 3.5%. Using binary superiority the estimated sample size is 110 breasts per group (110 patients) with significance b-alpha 5% and the power of 80% (1- beta). http://www.sealedenvelope.com/power/binary-superiority

Statistical analysis

Categorical variables are compared using a chi-square test, and the Student t-test is used to compare continuous variables between groups. Logistic regression with adjustment for other possible risk factors is used to estimate the odds ratios and 95% confidence intervals.

10.0 Privacy/Confidentiality Issues

Collected data will be stored in password protected database.

11.0 Follow-up and Record Retention

Blinding/Data Collection

Evaluation of the wound will be performed by experienced clinic nursing staff. The site of application of the CHG solution will not be disclosed during clinic visit to nursing staff. The collection of data will be provided Marcia Spear, DNP, ACNP-BC without of knowledge of drug use.

The data will be extracted form StarPanel and entered in a RedCap database. Collected data will include: type of infection (major or minor), side of occurrence, route of antibiotic administration (iv or PO), length of hospitalization, any surgical procedures (incision and drainage, debridement, TE removal), the need for long term iv antibiotic therapy, pathogen based on culture results, days till recovery, type and time of repeat reconstruction.

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Figure 1. TE-based breast reconstruction with creation of pectoral and serratus muscles pocket.

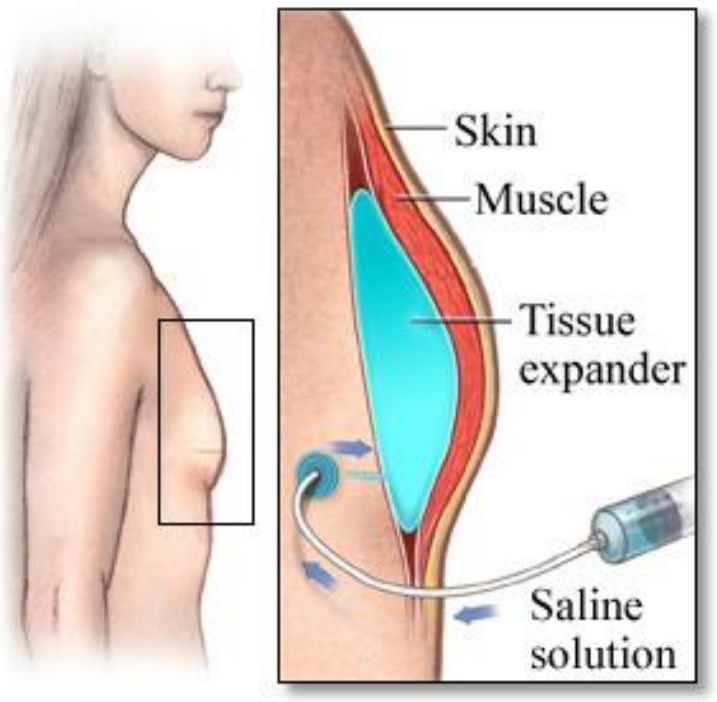

Figure 2. TE-based breast reconstruction with creation of surgical pocket with ADM sling