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ABSTRACT

Introduction In breast surgeries, prophylactic antibiotics given before the surgical incision as per Joint Commission Surgical Care Improvement Project guidelines have been shown to decrease the rate of postoperative infections. There is, however, no clear consensus on postoperative antibiotic prophylaxis in patients undergoing mastectomy with indwelling drains. This trial protocol proposes to study the difference in rates of surgical site infection (SSI) with or without continuation of postoperative antibiotics in patients undergoing mastectomy without immediate reconstruction and with indwelling drains.

Methods and analysis In this multicentre, double-blinded clinical trial, all patients undergoing mastectomy (without immediate reconstruction) will receive a single prophylactic dose of preoperative antibiotics at induction of anaesthesia and will then get randomised to either continue antibiotic prophylaxis or a placebo postoperatively, for the duration of indwelling drains. The primary and secondary outcomes will be development of an SSI and antibiotic-associated adverse effects, respectively. Data will be collected through a standard questionnaire by wound assessors. Intention-to-treat analysis will be carried out using STATA V.12. For categorical variables, frequencies and percentages will be assessed by χ^2 test/Fisher's exact test as appropriate. The quantitative variables will be computed by their mean±SD or median (IQR) and will be assessed by independent t-test/Mann-Whitney test as appropriate. Unadjusted and adjusted relative risk with their 95% CI will be reported using Cox proportional regression. A p value of <0.05 will be considered statistically significant.

Ethics and dissemination Ethical approval has been obtained from each site's Ethical Review Board. The study background and procedure will be explained to the study participants and informed consent will be obtained. Participation in the study is voluntary. All data will be deidentified and kept confidential. The study findings will be published in scientific media and authorship guidelines of International Committee of Medical Journal Editors will be followed.

Trial registration number NCT04577846. (patient recruitment)

Strengths and limitations of this study

- A pragmatic, multicentre, double-blinded, randomised control trial conducted at public and private tertiary care hospitals.
- Patients with comorbidities will not be excluded unless there is an absolute need for antibiotics postoperatively, thus results will be generalisable.
- Patients in this study are randomised using the block-randomisation technique due to which treatment groups are equal in size and are uniformly distributed as related to patient characteristics.
- The trial excludes patients undergoing immediate reconstruction as this procedure is not a commonly performed procedure in the developing world.

INTRODUCTION

Background

Worldwide, breast cancer comprises 10.4% of all cancer among women, making it the second most common cancer (after lung cancer) and the fifth most common cause

of cancer death. In Pakistan, breast cancer is the most common malignancy in women, accounting for approximately 40% of all malignant tumours. A study from Pakistan conducted at a tertiary care hospital reported that regardless of age, the majority of patients in their cohort presented with higher stage breast cancer than the comparison group of patients in the National Cancer Database, which is a hospital registry US database of over 1500 cancer centres.[1] The higher stage at presentation often leads to a greater likelihood of warranting a mastectomy rather than breast conservation surgery.

Reports of surgical site infections (SSIs) after breast surgery may range from 1% to 26%,[2–5] which is high for surgeries that are considered 'clean procedures', as defined by the Centers for Disease Control and Prevention (CDC) wound classification system. There is no clear consensus on the duration of prophylactic antibiotics in patients undergoing mastectomy, and practices may vary among breast and reconstructive surgeons. Prophylactic antibiotics given before surgical incision/procedures as per Joint Commission Surgical Care Improvement Project guidelines have been shown to decrease the rate of postoperative infections in a vast number of patients. However, the efficacy of prophylactic antibiotics used after surgeries is not known.[6–9] Therefore, most guidelines recommend a single dose of periprocedural antibiotics, and prolonged continuation after surgery has been discouraged. The use of common or more specific antibiotics for the duration of drains being in place is controversial.

The drains used following breast surgeries are closed suction, and they are retained for a variable duration depending on the volume of effluent. The likelihood of microorganisms contaminating these drains increases with longer presence and may result in SSI, yielding the same organisms as found in the drains.[4 9] Evidence regarding the risk of SSI with the use and duration of indwelling drains is controversial.[4 9–15] Surgical drains are commonly removed when output is less than 30 mL/24 hours, often 5–7 days later; however, some patients can have drains in place for weeks before meeting the criteria for removal.[16]

Recent national/international clinical guidelines recommend the use of a single dose of preprocedural antibiotics for mastectomy patients with or without drains.[17 18] The American Society of Breast Surgeons also does not recommend the continuation of postsurgical antibiotics in the absence of relevant indicators, such as purulent drainage from the incision or drain site, tenderness, localised swelling, erythema or warmth, and clinical diagnosis of cellulitis.[19] Even in the setting of immediate breast reconstruction following mastectomy, there is insufficient evidence for the use of extended prophylactic antibiotics to reduce SSI rates. However, the meta-analysis also pointed out that, in general, antibiotics were not used uniformly in terms of regimens, timing, dosing, and duration.[20]

Lack of clear consensus and absence of universal guidelines regarding postoperative continuation of prophylaxis results in significant practitioner variation. In a study by Brahmbhatt *et al*,[21] 16% of practitioners reported that, most of the time, they use postoperative antibiotics as prophylaxis; in contrast, 76% responded that they never use postsurgical prophylaxis for more than 24 hours in patients without reconstruction. The length of prolonged, postoperative antibiotics may also vary by practitioners, some using a predefined regimen of about 2–7 days while others continue them until the drains are removed.

Rationale

There is no clear consensus regarding the continuation of postoperative antibiotic prophylaxis following breast surgeries, consequently significant practitioner variation exists globally. Various studies have failed to establish the impact of postoperative antibiotic prophylaxis on rates of SSIs, thus a prospectively designed phase III clinical trial is essential to provide higher level evidence. We propose to study the difference in rates of SSI in a double-blinded, multicentre trial by randomising patients undergoing mastectomy (without immediate reconstruction and with indwelling drains) to be randomised to either continuing prophylactic antibiotics or receiving a placebo postoperatively. All will receive a single dose of prophylactic antibiotic preoperatively.

Objectives

1. To determine the rates of SSI in patients in the two arms of this trial, in which all patients will receive the first prophylactic preoperative antibiotic dose at induction of anaesthesia and then be randomised to:
   a. Receive a placebo every 8 hours, as long as there is/are drains(s) in place.
   b. Continue receiving prophylactic antibiotic every 8 hours for the duration of indwelling drains.
2. To identify factors associated with differing rates of SSI in the intervention and control group.

Trial design

This is a two-armed, randomised, double-blinded placebo control clinical trial. The study participants will be women, 18 years and older, who are planned to undergo mastectomy without immediate reconstruction and will have indwelling closed suction drain(s). We used the Standard Protocol Items: Recommendations for Interventional Trials checklist when writing this protocol.[22]

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOME

Study setting

This study will be conducted at three sites:

Site 1: Aga Khan University Hospital (AKUH), Karachi, Pakistan, a tertiary care private hospital.

Site 2: Liaquat National Hospital (LNH), Karachi, Pakistan, a tertiary care private hospital.

Site 3: DOW University of Health Sciences (DUHS), Karachi, Pakistan, a public sector hospital.

Eligibility criteria

Inclusion criteria: this trial will include all the patients who are:

- Women, 18 years and older, who are planned for mastectomy by a breast surgeon at one of the study sites, that is, AKUH, LNH or DUHS, and who will have indwelling closed suction drain(s) postoperatively.
- Women who will give consent to participate in the study.

Exclusion criteria: this study will exclude all those patients who will:

- Undergo immediate breast reconstruction. The healthcare payment model in the developing world, including Pakistan, is fee-for-service in which a patient pays for each individual medical care service, including reconstruction. Subsequently, reconstruction is an expensive procedure, which poses a huge financial burden for a majority of patients. Additionally, locally advanced breast cancer is more prevalent in our setting than the developed world in the West, warranting postmastectomy radiation, which often leads us to recommend delayed reconstruction as the preferred option. Thus, most patients who undergo mastectomy either do not elect or are not ideal candidates for immediate reconstruction.
- Have other medical indications for which they must remain on antibiotics for more than the single preoperative dose.
- Have any history of allergies to beta-lactam drugs or iodine.
- Had an open breast or axillary biopsy/breast conservation in the last 30 days on the ipsilateral side.

Interventions: description, modifications and adherence

Description

Treatment arm

Standard care 1 g intravenous cefazolin given preoperatively at induction of anaesthesia followed by a course of 500 mg oral cephalexin given every 8 hours for the duration of the indwelling drains.

Control arm

Standard care 1 g intravenous cefazolin given preoperatively at induction of anaesthesia followed by a course of oral placebo capsules (identical in physical appearance to the antibiotic) given every 8 hours for the duration of the indwelling drains.

The investigational product will be stored in the Clinical Trial Unit (CTU) research pharmacy with controlled access under the direct supervision of the CTU pharmacist. The CTU pharmacist in the presence of the study team personnel will verify the expiry and lot/batch number at the time of receiving. The expiry date and the batch number will be documented in the pharmacy logs (investigational product/supplies inventory and expiry log). All unused investigational products collected from patients will be returned to the CTU pharmacy. The CTU pharmacist will also keep track of inventory and will notify the principal investigator and study coordinator when the investigational product (IP) needs to be restocked.

Study flow

Three research assistants, one for each site, are medical and dental graduates (with experience of facial wounds), who would be trained in the Centre for Disease Control (CDC) wound assessment criteria for SSIs by the principle investigator (PI) and the co-PI (an infectious disease specialist) over a 2-week period prior to initiating the trial. Research assistants would also be required to shadow the PI in the clinics for a week to have uniform training regarding wound assessment, before initiation of the trial. Also, a research coordinator will liaise with the research assistants and will be coordinating the study at all three sites. The research coordinator will ensure an adequate supply of the study drug as well as placebo prepared by the AKUH pharmacy to be dispensed to the CTUs of respective institutions. At each of the three sites, a consistent approach to monitoring/documentation of SSI as well as adverse outcomes will be ensured by the research team.

All patients who are consented and booked for mastectomy (without reconstruction) by the participating surgeons of AKUH, LNH and DUHS will be screened by trained research assistants during the outpatient preoperative clinic visit (online supplemental appendix 1). The eligible and consented participants will then be randomised preoperatively by the CTU pharmacist (as above) using a computer-generated randomisation list, to either the intervention or control arm.

At the time of surgery, standardised skin preparation will be performed for both arms before the incision by the surgical team. The prep will consist of:

1. Povidone iodine 0.75 % W/V with normal saline hand scrub.
2. Iodine preparation paint.
3. Cefazolin 1 g intravenous preoperatively at the induction of anaesthesia.

Postsurgery

1. The intervention arm will be administered oral cefalexin 500 mg every 8 hours, which will be continued for the duration of the indwelling drains (usually 14 days).
2. The control arm will be administered an identical in appearance placebo capsule filled with inert material for the duration of the drains.
3. All study medications, that is, antibiotic/placebo, will be dispensed by the CTU pharmacist.

Wound assessment

1. SSI will be assessed by the treating surgeon and the wound assessor (trained research assistants) during the follow-up visits. The research assistants will be doing

their independent wound assessment without being influenced by the surgeon. The data collection form has separate areas to document findings of surgeons as well as the wound assessor for independent evaluations.
2. The first postoperative visit will be on postoperative day 5±2 days (3–7 days) and subsequently at each routine postoperative visit while the drain is in place. As per CDC guidelines, the day of the procedure will be considered postoperative day 1. Rates of SSI will be collected up to the 90th postoperative day. If the patient does not have a routine clinic visit scheduled on day 90, the wound assessor (trained research assistant) will call the patient over the phone to inquire about the status of the wound. If need be, the patient will be asked to come in for a wound evaluation.
3. Rates of drug-related adverse effects will be documented.

Data will also be collected on the patient's clinical factors potentially relevant to SSI, including smoking status (as never smoker, prior smoker and patients who quit smoking within the last 60 days before surgery), patient's age, body mass index (BMI; >30 is defined as a marker of obesity) diabetes mellitus and recent corticosteroid use (inhaled/oral), prior ipsilateral breast/axillary surgery in the last 60 days, neoadjuvant chemotherapy, prior radiation to the ipsilateral breast and patients with active tuberculosis, HIV or on immunosuppression. Data will also be abstracted on the type of surgery performed defined as:

a. Unilateral/bilateral mastectomy.
b. Associated axillary surgery (none, sentinel lymph node biopsy, axillary sampling or axillary dissection).
c. The procedural length will be recorded in minutes from the start of incision to completion of skin closure.
d. Type of skin closure (staples vs subcuticular).
e. Duration of drain retention (counting day of surgery as day 1).
f. Duration of hospital stay, counting the day of admission as day 1.
g. Other constant variables will be additionally evaluated as dichotomous categorical variables, that include BMI >30, hospital stay >1 day, drain duration >14 days and having more than one drain in situ. Length of the stay >1 day is selected for comparison as most of our patients are discharged the day after the procedure at our institute. Age will be additionally evaluated categorically by decade (online supplemental appendix 2).

Modification

Discontinuation from the study

1. Any adverse effects as perceived (by the treating surgeon) to be related to the study drug. This includes, but is not limited to, rash and diarrhoea.
2. Development of a wound infection while on the study drug (the patient will exit the study and the infection will be treated and counted as the outcome).
3. Need for reoperation on the same site within 30 days of the mastectomy (except for when reoperation is for infection, in which case the patient will exit the study, but the infection will be counted as the outcome).

Adherence

Subject compliance will be monitored by the CTU pharmacist, by counting the returned study drug/capsules as well as by reviewing the compliance log maintained by the patient. An additional compliance log will be maintained by the primary investigator/study team after a reminder telephone call to the participants in each group. This phone call will be made to reinforce the instructions and the need to maintain the log, as well as for reassurance. (online supplemental appendix 3).

Outcomes

Primary outcome: SSI (time frame: up to 90 days).

Standard CDC criteria:[23]

1. Purulent drainage from the incision or drain site.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue.
3. Deliberate opening of the incision by a surgeon in patients having either tenderness, localised swelling, redness or warmth.
4. Diagnosis of SSI by the surgeon or study wound assessor.
5. Prescription of therapeutic antibiotics.
6. Patients clinically diagnosed and documented to have cellulitis.

Other outcome measures

Rates of antibiotic-associated side effects (time frame: will be assessed during the follow-up visits between postoperative days 3 and 7 for the first postoperative visit and subsequently at each routine postoperative visit while the drain is in place, for a maximum of 90 days).

Participant timeline

Patients will be enrolled preoperatively, after consenting to the surgical procedure. Research assistants will screen/consent the patient and liaise with the CTU to arrange for the relevant study drug. All study patients (in both arms) will receive the preoperative antibiotic prophylaxis at the time of induction. The postoperative antibiotic/placebo doses will be administered to the patient at an interval of 8 hours and will continue for the duration of the indwelling drains. Patients will be followed for 90 postoperative days, counting the day of the surgery as day 1. At each follow-up visit, the patient will be assessed both by the primary surgeon/another covering study surgeon as well as the wound assessor (trained research assistant). Over the phone, follow-ups will be done by the wound assessor (trained research assistant) only.

Sample size calculation

The sample size was calculated in OpenEpi software V.3.01. The minimum sample size that will be required is 384 patients who have undergone mastectomy with indwelling drains. Of these, 192 patients will be those with a single dose of prophylactic preoperative antibiotic

and prolonged use of prophylactic postoperative oral antibiotics (intervention arm), and 192 participants will be those with a single dose of prophylactic preoperative antibiotic with placebo (control arm), with inflation of 10% in both the groups for non-response rate. An anticipated incidence of surgical site infection (SSI) of 3.4% in the intervention arm and 9.2%–14% in the control arm,[4 24] with a 5% level of significance and power of 80% to detect a 9% reduction of infection in intervention arm versus the control. Since we will be recruiting participants from three study sites, we applied proportionate sampling to estimate the sample size for each group. In this technique, the sample size of each site is proportionate to the total population size, which was 565. We calculated the per cent (weight) for each group by taking a ratio of the number of individuals in each group and the total population. Hence, we will require a minimum sample of 66 women in the intervention arm and 66 women in the control arm from AKU, 85 women in the intervention arm and 85 women in the control arm from LNH, and 41 women in the intervention arm and 41 women in control arm from DUHS campus.

METHODS: ASSIGNMENT OF INTERVENTIONS (CONTROLLED TRIAL)

Allocation: sequence generation, concealment mechanism and implementation

The PI's research fellow will serve as the research coordinator and will be responsible for coordination with the specially hired and trained wound assessors/trained research assistants. At each of the three study sites, the research assistants will be responsible for recruiting participants, obtaining the study drug from the CTU and delivering it to the patient, giving instructions and following up on the wound status as well as for study drug compliance. The research assistants will receive adequate training from the principal investigator.

Randomisation will be performed by the block randomisation method. Patients will be allocated to one of the following groups:

Group 1 (intervention arm): will be those patients who will receive a single dose of prophylactic preoperative antibiotic (cefazolin 1 g intravenously preoperatively), then continue with oral cefalexin (capsule) 500 mg every 8 hours, for the duration of the drains, which usually is about 14 days.

Group 2 (control arm): will be those who receive a single dose of prophylactic preoperative antibiotic (cefazolin 1 g intravenously preoperatively). Postoperatively, these patients will receive a capsule filled with inert material every 8 hours (placebo capsule, which will be identical in appearance to the study antibiotic).

Randomisation will be performed via computer-generated random numbers by the AKUH CTU pharmacy.

Blinding (masking)

This study is a double-blinded randomised controlled trial as our participants and the treating surgeon/wound assessor (trained research assistant) will be blinded to the group that each participant will be assigned to. As an additional measure to maintain blinding, both the study antibiotic and placebo will be dispensed by the CTU in capsules that have an identical appearance.

Blinding (masking): emergency unblinding

Unblinding can be done in the following situations:

1. Accidental unblinding.
2. Unblinding due to any serious adverse event (SAE).

In either case, the principal investigator will promptly document and explain any unblinding to the sponsor and the Ethics Review Committee (ERC). If a patient's treatment assignment is unblinded, the patient will remain in the study and continue the protocol-specified follow-up evaluations.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection plan

The outcome assessment (SSI) will be performed by the treating surgeon and the wound assessor (trained research assistant) during the follow-up visits. The data on the patient's demographics and other disease-related information will be collected on a structured questionnaire. The data collection form can be made available from the corresponding author on reasonable request.

Data collection plan: retention

All this information will be maintained at the CTU AKUH.

Data management

The data will be entered in Redcap software. The data will be double entered and range checks will be entered to maintain the quality of the data. The database is authorised only to the principal investigator. The database can be made available from the corresponding author on reasonable request.

Statistics: analysis population and missing data

We plan to do the intention-to-treat analysis as mentioned in the plan of analysis. The missing data will be dealt with by imputation. The analysis will be performed using STATA V.12. Descriptive statistics will be computed for categorical variables by computing their frequencies and percentages and will be assessed by χ^2 test/Fisher's exact test as appropriate. The quantitative variables will be computed by their mean±SD or median (IQR) and will be assessed by independent t-test/Mann-Whitney test as appropriate. Unadjusted and adjusted relative risk with their 95% CI will be reported by using Cox proportional regression. All plausible interactions will also be assessed. Intention-to-treat analysis will be carried out. A p value of <0.05 will be considered statistically significant throughout the study.

METHODS: MONITORING

Data monitoring: formal committee

The data monitoring team of AKUH CTU (principal site) will overlook the trial. This data monitoring committee overlooks all the trials that take place at the Aga Khan University and is independent of the sponsors. Further details of its key services and ancillary services can be found online (https://www.aku.edu/ctu/services/Pages/home.aspx).

Data monitoring: interim analysis

The data and safety monitoring committee, composed of an independent group of experts in the involved fields (biostatistician, clinical researcher, epidemiologist and a clinician with expertise in the disease under investigation), will conduct an interim analysis. If significantly high rates of SSI in one group compared with the other at interim analysis is observed, the trial will be stopped.

Harms

Adverse events

In the event of an adverse effect, study participants will be instructed to report to their treating surgeon immediately. The primary surgeon will then assess if the symptoms are an adverse drug effect and recommend withdrawal from the study if deemed so. The anticipated drug adverse could be events, such as a drug allergy, *Clostridium difficile* or antibiotic-associated diarrhoea. Only <5% of patients develop allergy due to cephalosporin use; similarly, there is inconsistency regarding the relationship of *C. difficille*-associated diarrhoea with cephalosporin use.[25–27] Investigations pertaining to the adverse drug effect may include, but are not limited to, complete blood counts and stool test (for suspected *C. difficille*). The adverse events (AEs) will be recorded and reported to ERC within a specified period. A patient thought to have an adverse reaction will exit the trial at this point. Management given for the AE/SAE will be documented in the study documents. All drug accountability will be maintained in the CTU. If the patient is withdrawn from the study, they will be encouraged to complete the follow-up visits and data will be collected for the follow-up visit.

Assessment of safety

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment will also be documented. An AE can, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. All study-related adverse/serious AEs will be managed and reported to the ERC, medical affairs and pharmacy. The principal investigator and study coordinator will follow-up on any AEs and SAEs. The type and duration of the follow-up of subjects after AEs will be defined by the PI.

Reporting and recording of procedures of adverse events

The PI will report all AEs in case report form (CRF)/Data Clarification form (DCF), AE reporting form to the sponsor (in the specified time) and to the ERC. SAE will be reported to the sponsor via telephone, email, and/or fax within 24 hours. Confirmation will be ensured and documented. The immediate report will be followed by a detailed written report on the event and SAE/AE form along with supporting documents will be submitted to the study sponsor and ERC no later than 7 days from notification of the event. The PI will also report to relevant authorities within 15 calendar days after SAE/unanticipated AE that may be related to the study protocol. The PI will also be responsible for reporting all serious or unexpected AE to ERC within 7 days from notification of the event. Requests from the sponsor/ERC for further information of the SAE will be promptly responded to.

Patients will be withdrawn from the study due to:

1. Withdrawal of consent by the patient or legal guardian.
2. Development of any AE or SAE.
3. Investigator decision that, in the interest of the patient, it is not medically acceptable to continue the patient's participation in the study.
4. Termination of the study by the sponsor.

If the patient withdraws from the study, the principal investigator will promptly document and inform the sponsor about the termination from the study within 48 hours. Despite withdrawing from the study, patients will be encouraged to complete the follow-up visits and data will be collected for the follow-up visit. Participants who will withdraw or will be terminated from the study will not be replaced as the sample size is calculated keeping in view the 10% non-response rate.

Auditing

The audit of the trial is usually conducted by the ERC (and sometimes by Joint Commission International) who are independent from the investigators and the sponsors.

Ethics and dissemination

Research ethics approval

Ethical approval has been obtained from the ERC of all three study sites that is, the Aga Khan University, Karachi's ERC, and ERC at LNH and DUHS. The study will be conducted according to the Consolidated Standards of Reporting Trials guidelines (figure 1) and guidelines of the World Medical Association's Declaration of Helsinki and the principles of Good Clinical Practice (GCP). The study background and procedure will be explained to the study participants and informed consent will be obtained. Participation in the study is voluntary. All data will be deidentified and will be kept confidential. The study findings will be published in the scientific media and the authorship guidelines of International Committee of Medical Journal Editors (ICMJE) will be followed.

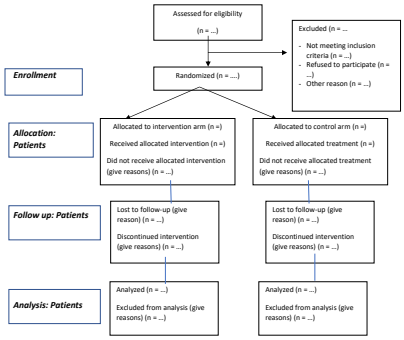

Figure 1 Consolidated Standards of Reporting Trials 2010 flow diagram.

Protocol amendments

Any amendment in protocol will be submitted to the ERC and regulatory authorities for approval, and the trial will be conducted in compliance with regulations reporting, 6-month/annual safety and progress reports, and a copy of the final study report will be submitted to the ERC and funding agency.

Consent or assent

Participants will be recruited from AKUH, LNH and DUHS. Written informed consent will be obtained from the participants by trained research assistants/data collectors (online supplemental appendix 4). They will be explaining the study procedure in detail to the study participants along with the risks and benefits associated with taking part in the study. The data collectors will be trained by the PI and co-investigators. Randomisation for all study sites will take place at the CTU AKUH.

Confidentiality

Strict confidentiality and privacy rules will be followed. Patients will be informed that all information will be kept confidential. All study materials containing personal identifiers will be kept in a locked file cabinet. A unique study identification number will be assigned to each participant. Data will be entered from the hard copy into the electronic database that will be password protected and only accessed by the research staff of this study. As per GCP guidelines, data will be retained for 15 years. The participation of the participants will be voluntary.

Data access

The principal investigator and other authors of the study will have access to the final data set.

Ancillary and post-trial care

The cost of all the AEs will be borne by the study budget.

Dissemination policy: trial results

The study findings will be disseminated to different stakeholders, such as healthcare professionals through publications in local, national and international journals, presentations at conferences and workshops, and research briefs.

Dissemination policy: authorship

We will follow the authorship guidelines of ICMJE for authorship eligibility. At the moment, we do not intend to use any professional writers. However, if the journal suggests reaching out to English proofreading experts, we will seek professional assistance.

Dissemination policy: reproducible research

Materials that are described in this manuscript pertain to the study protocol and no raw data is being reported. The data set will be collected and analysed and can be made available from the corresponding author on reasonable request.

Patient and public involvement

It was not possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Strengths and limitations of the study

First, this will be a multicentre study, including both public and private tertiary care hospitals catering to patients from different socioeconomic backgrounds. Hence, our study results will be generalisable to all mastectomy patients who have drains in place and have not undergone reconstruction. Moreover, to the best of our knowledge, this will be the first study from our context. Finally, the pragmatic approach will allow easy applicability to the current practice of individuals across a wide range of clinical settings. One of the limitations of our study is that patients with reconstruction will be excluded to prevent variability in outcomes.

Study implications

Through this study, we will be able to identify the most effective prophylactic regimen to reduce rates of SSI among mastectomy patients with indwelling drains, hence it will lead to informed decision-making. The results will be widely generalisable and applicable worldwide.

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Contributors AS, NZ, HS, RS, OS and FM were involved in the conception of the design; acquisition, analysis and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; approving the final version to be published; and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REFERENCES

1 Zeeshan S, Ali B, Ahmad K, *et al*. Clinicopathological features of young versus older patients with breast cancer at a single Pakistani institution and a comparison with a national us database. *J Glob Oncol* 2019;5:1–6.
2 Vilar-Compte D, Jacquemin B, Robles-Vidal C, *et al*. Surgical site infections in breast surgery: case-control study. *World J Surg* 2004;28:242–6.
3 Throckmorton AD, Hoskin T, Boostrom SY, *et al*. Complications associated with postoperative antibiotic prophylaxis after breast surgery. *Am J Surg* 2009;198:553–6.
4 Degnim AC, Scow JS, Hoskin TL, *et al*. Randomized controlled trial to reduce bacterial colonization of surgical drains after breast and axillary operations. *Ann Surg* 2013;258:240–7.
5 Angarita FA, Acuna SA, Torregrosa L, *et al*. Perioperative variables associated with surgical site infection in breast cancer surgery. *J Hosp Infect* 2011;79:328–32.
6 Seo SK. An updated meta-analysis on the effectiveness of preoperative prophylactic antibiotics in patients undergoing breast surgical procedures. *Breast Diseases: A Year Book Quarterly* 2013;24:161–2.
7 Cochrane LibraryJones DJ. Prophylactic antibiotics to prevent surgical site infection after breast cancer surgery, 2014. Available: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005360.pub4/full
8 Specifications manual for joint commission national quality core measures [Version B1, July 2010] https://www.jointcommission.org/-/media/tjc/documents/resources/hai/implementation_guide_for_npsg_ssipdf.pdf
9 Felippe WAB, Werneck GL, Santoro-Lopes G. Surgical site infection among women discharged with a drain in situ after breast cancer surgery. *World J Surg* 2007;31:2293–9.
10 Gao Y-xu, Xu L, Ye J-ming, *et al*. Analysis of risk factors of surgical site infections in breast cancer. *Chin Med J* 2010;123:559–62.
11 Vilar-Compte D, Rosales S, Hernandez-Mello N, *et al*. Surveillance, control, and prevention of surgical site infections in breast cancer surgery: a 5-year experience. *Am J Infect Control* 2009;37:674–9.
12 Teija-Kaisa A, Eija M, Marja S, *et al*. Risk factors for surgical site infection in breast surgery. *J Clin Nurs* 2013;22:948–57.
13 Thomson DR, Sadideen H, Furniss D. Wound drainage after axillary dissection for carcinoma of the breast. *Cochrane Database Syst Rev* 2013;10:CD006823.
14 Rotstein C, Ferguson R, Cummings KM, *et al*. Determinants of clean surgical wound infections for breast procedures at an oncology center. *Infect Control Hosp Epidemiol* 1992;13:207–14.
15 Rey JE, Gardner SM, Cushing RD. Determinants of surgical site infection after breast biopsy. *Am J Infect Control* 2005;33:126–9.
16 Throckmorton AD, Boughey JC, Boostrom SY, *et al*. Postoperative prophylactic antibiotics and surgical site infection rates in breast surgery patients. *Ann Surg Oncol* 2009;16:2464–9.
17 Bratzler DW, Dellinger EP, Olsen KM, *et al*. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Surg Infect* 2013;14:73–156.
18 Hedrick TL, Smith PW, Gazoni LM, *et al*. The appropriate use of antibiotics in surgery: a review of surgical infections. *Curr Probl Surg* 2007;44:635–75.
19 Consensus guideline on preoperative antibiotics and surgical site infection in breast surgery;6 https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Preoperative-Antibiotics-and-Surgical-Site-Infection-in-Breast-Surgery.pdf
20 Hai Y, Chong W, Lazar MA. Extended prophylactic antibiotics for mastectomy with immediate breast reconstruction: a meta-analysis. *Plast Reconstr Surg Glob Open* 2020;8:e2613.
21 Brahmbhatt RD, Huebner M, Scow JS, *et al*. National practice patterns in preoperative and postoperative antibiotic prophylaxis in breast procedures requiring drains: survey of the American Society of breast surgeons. *Ann Surg Oncol* 2012;19:3205–11.
22 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
23 Control CfD, Prevention. Surgical site infection event SSIS. Guidelines and procedures for monitoring SSI. 2014 - Google Search, 2021. Available: https://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf
24 Edwards BL, Stukenborg GJ, Brenin DR, *et al*. Use of prophylactic postoperative antibiotics during surgical drain presence following mastectomy. *Ann Surg Oncol* 2014;21:3249–55.
25 Wilcox MH, Mooney L, Bendall R, *et al*. A case-control study of community-associated Clostridium difficile infection. *J Antimicrob Chemother* 2008;62:388–96.
26 Wilcox MH, Chalmers JD, Nord CE, *et al*. Role of cephalosporins in the era of Clostridium difficile infection. *J Antimicrob Chemother* 2017;72:1–18.
27 Thomas C, Stevenson M, Riley TV. Antibiotics and hospital-acquired Clostridium difficile-associated diarrhoea: a systematic review. *J Antimicrob Chemother* 2003;51:1339–50.