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ORIGINAL ARTICLE – BREAST ONCOLOGY

Randomized Controlled Trial to Reduce Bacterial Colonization of Surgical Drains with the Use of Chlorhexidine-Coated Dressings After Breast Cancer Surgery

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ABSTRACT

Background. Breast surgery is considered a clean surgery. However, surgical-site infection (SSI) rates are currently higher than predicted. Postoperative drains remain in situ for several days, with inevitable bacterial colonization and increased SSI risk.

Methods. This randomized controlled trial from October 2016 to January 2018 analyzed patients undergoing breast cancer surgery. The patients were randomized to either the standard drain care group or the antiseptic dressing group (3M® Tegaderm® CHG). Drain samples taken on postoperative days (PODs) 7 and 14 were cultured as standardized in the laboratory. Colonization rates and SSI were compared between the two groups.

Results. The study enrolled 104 patients with 167 surgical drains. The patients' clinical characteristics were similar in the two groups, with no statistically significant differences. Bulb fluid cultures at postoperative week (POW) 1 were positive for 42.9% of the control group and 28.9% of the antiseptic group ($p = 0.06$). Cultures from the POW 2 assessment were positive for 79.7% of the control group versus 54.9% of the antiseptic group ($p = 0.001$). Cultures from drain tubes were positive for 79.8% of the control group and 50.7% of the antiseptic group ($p = < 0.001$). In 11 patients, an SSI developed, 3 (5.8%) from the intervention and 8 (15.4%) from the control procedure ($p = 0.11$).

Conclusion. The study findings demonstrated that the use of antiseptics at the drain exit site significantly reduced bacterial colonization of the closed drainage system in breast cancer surgery. Semi-permeable occlusive chlorhexidine-impregnated dressings provide an opportunity to test simple, safe, and low-cost interventions that may reduce drain bacterial colonization and SSI after breast surgery.

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Breast cancer is the most common neoplasm among women. The treatment is multimodal, and surgery is the cornerstone.[1–3] The most common complications are seromas and surgical-site infections (SSIs).

Because mastectomy is considered a clean surgery, low rates of infection are expected.[4] However, studies show that the occurrence of infection may be higher than expected, with SSI rates reaching 19%.[5–10]

Obesity, diabetes mellitus, prior radiotherapy, and smoking are risk factors for SSI.[11–14] In breast surgery, drains may remain for prolonged periods, up to 3 weeks, with a higher risk of bacterial colonization and SSI.[15,16] Recently, chlorhexidine-impregnated dressings at the drain exit site and antisepsis of the drainage bulb with sodium hypochlorite solution after axillary, mastectomy, and immediate prosthetic breast reconstruction have demonstrated a decrease in colonization and lower rates of SSI.[17,18]

At our institution, radical mastectomy is a frequent procedure, with prolonged use of drains. Despite the implementation of several preventive strategies, the SSI rate remains between 12 and 15%.

We hypothesized that bacterial colonization of surgical drains contributes to SSI after breast cancer surgery and that local antisepsis with chlorhexidine dressings might decrease drain colonization and SSI in patients with prolonged use of drains.

METHODS

Design and Location

We conducted a prospective, open-label, randomized controlled trial at the Instituto Nacional de Cancerología (INCan), a 133-bed nationally referenced teaching cancer center in Mexico City. The study was approved by the Institutional Review Board (016/040/1Nl) (CEI/1090/16) and registered at clinicaltrials.gov (NCT03229824).

Population

The study enrolled patients between October 2016 and January 2018 with confirmed breast cancer undergoing total mastectomy (TM), modified radical mastectomy (MRM), and/or breast-conserving surgery (BCS) involving axillary lymph node dissection (ALND), with or without immediate reconstruction with tissue expander (IRTE). Patients were excluded if they were pregnant or breast-feeding, were not willing to complete 30 days of follow-up assessment, had undergone breast surgery 3 months previously, had received antibiotics within 14 days before of surgery, had a known allergy to chlorhexidine, prior radiotherapy, had immediate reconstruction with autologous tissue, or had cognitive impairment or language barriers. Patients also were excluded if they had received antibiotics other than those established for perioperative antibiotic prophylaxis.

Sample Size

To detect a bacterial colonization rate of 30% in drainage fluid at postoperative week (POW) 1 in the control group and 60% in the intervention group with 80% power and 0.05 α, a sample size of 104 was projected.

Randomization

The patients were randomized immediately before surgery and allocated either to impregnated chlorhexidine-dressing treatment (chlorhexidine group) or to the standard care procedure (control group) through Sealed Envelope Ltd. Randomization stratified the patients by surgical procedure to either radical surgery (TM, MRM) or BCS with ALND. The patients with bilateral cancer received the same intervention for both sides. The operating surgeon was blinded to the allocation until the end of surgery. Randomization was performed by a non-investigation-related team.

Perioperative Standardization

All the patients received a single dose of intravenous preoperative cephalotin 2 g (selected instead of cefazolin because it is not widely available in Mexico) or cefuroxime 1.5 g 30 to 60 min before surgical incision. Antibiotic redosification was performed intraoperatively as needed. In case of an allergy to cephalosporin, clindamycin 900 mg was permitted. Surgical drains (Biovac 10 mm; Biometrix Ltd Kiryat Mada, Jerusalem, Israel) were set in place as usual.

Intervention and Drain Care Regimens

Patients and family members received written instructions on wound and drain care before the patient's discharge. Individuals in both arms of the study were instructed to clean the wound, strip the drain tubing with 70% alcohol wipes, empty the bulb, and record fluid volume every 12 h until the drain was removed. The control patients were instructed to clean the drain exit site with 70% alcohol wipes.

The chlorhexidine-group procedure consisted of placing a 2% chlorhexidine-impregnated dressing (3M® Tegaderm® CHG) at the drain exit site at the end of surgery. A team member changed the dressing 7 days after surgery. At each postoperative visit, the wound was checked, and daily records on drain fluid were verified. We also verified that patients were compliant with instructions.

Drain removal and sample collection was performed by a member of the research team. The drain exit site was cleaned with alcohol before the inner portion was cut with

a sterile scalpel. Two members of the research team were trained to perform this procedure under aseptic conditions. Each drain was evaluated separately for bacterial colonization end points and treated according to the allocation group.

Follow-Up Visits and Cultures

Demographic- and surgery-related variables were collected prospectively from the electronic medical chart. The patients were followed daily while in the hospital, then weekly until postoperative day (POD) 30, infection, or the resolution of other complications if these occurred. At POWs 1 and 2, the investigator evaluated the patient's clinical status, surgical wound characteristics, fluid volume, and drain care. Adverse events related to the Tegaderm CHG 3M dressing were assessed at each visit. For the patients who had immediate breast reconstruction with tissue expanders (IRTE), surveillance was expanded to 1 year or earlier if the expander was removed or if the reconstruction was completed. Drain removal was considered if the fluid was less than 30 ml in the previous 48 h.

If an SSI[19] was suspected, samples were taken for microbiologic studies and appropriate empirical antimicrobial therapy was initiated. The SSIs included any of the following within 30 days after the operation or up to 1 year for patients with immediate reconstruction with tissue expander: purulent drainage, positive aseptically collected culture from the wound or surgical site, signs of inflammation with the opening of an incision with a negative culture, or physician diagnosis of infection, which could include cellulitis. Cases of equivocal SSI were reviewed in detail and discussed by the research team, then decided by consensus.

Microbiology

To determine bacterial colonization, microbiologic analysis of the drain bulb fluid and the drain tube were performed at POWs 1 and 2. A 3-ml sample of the drain bulb fluid was collected under aseptic conditions. Samples were inoculated onto sheep blood 5% agar, MacConkey, chocolate, and Sabouraud dextrose agar with antibiotic. Sheep blood and MacConkey agars were incubated in an aerobic atmosphere at 37 °C. Chocolate agar was incubated under carbon dioxide (CO_2) conditions at 37 °C, and Sabouraud dextrose agar was incubated at 30 °C. The plates were incubated for 48 h or until growth. Fluid cultures with more than 100,000 colony-forming units (CFU) per milliliter were considered positive.

The drain's inner portion (3–4 cm) was cut with a sterile scalpel and processed by a semi-quantitative technique onto sheep blood and Sabouraud dextrose agar plates. Once the rolling was completed, the tip of the drain was introduced into a tube with 5 ml of sterile saline solution. The tube was sonicated for 1 min in a Bransonic ultrasonic cleaner (Branson 3510; Branson, Danbury, CT, USA) and shaken for 15 s before the plates were inoculated. A 100-μL sample from the suspension was inoculated onto the sheep blood, Sabouraud, and MacConkey agars. A drain-tubing culture was positive with 15 CFU/ml or more.

An aliquot of fluid and drain-tip sonication fluid was used to determine bacterial load by real-time polymerase chain reaction (PCR) using the *16S* gene as the housekeeping gene and SYBR Green as the amplicon detector. Details of the real-time PCR are described in the Supplementary Material.

Species were identified according to the standardized laboratory procedure with use of semi-automated equipment (VITEK2; bioMérieux, Inc., Hazelwood, MO, USA). The microbiology laboratory staff was blinded to patient allocation.

Statistical Analysis

All randomized patients were analyzed by means of intention-to-treat and per protocol analysis. We compared clinical- and surgical-related variables using the Pearson Chi square for categorical variables and the Mann–Whitney *U* test or Student's *t* test for continuous variables, as appropriate.

The primary end point of the study was bacterial colonization in drainage bulb fluid at POW 1. Drain bulb fluid colonization at POW 2 and drain tubing colonization were secondary end points. Colonization rates were analyzed on a per drain level, and SSI rates were analyzed using the Pearson Chi square test. A p value lower than 0.05 was considered statistically significant. In the colonized samples, each isolated microorganism was considered a unit for the quantitative analysis.

Due to the limitation of using pre-specified cutoffs to define a positive culture for drain cultures, quantitative real-time PCR was performed to quantify bacterial load. Bacterial load was analyzed by the Mann–Whitney *U* test. Analysis was performed using Statistical Program for Social Sciences, version 24.0 statistical software (SPSS; IBM Corp., Armonk, NY, USA).

RESULTS

The study enrolled 116 patients, but 12 of the patients (10.34%) did not complete the study follow-up assessment (Fig. 1). The study follow-up period was completed by 104 patients (89.6%), with 167 surgical drains evaluated. The mean age of the patients was 53.38 ± 12.36 years, with no

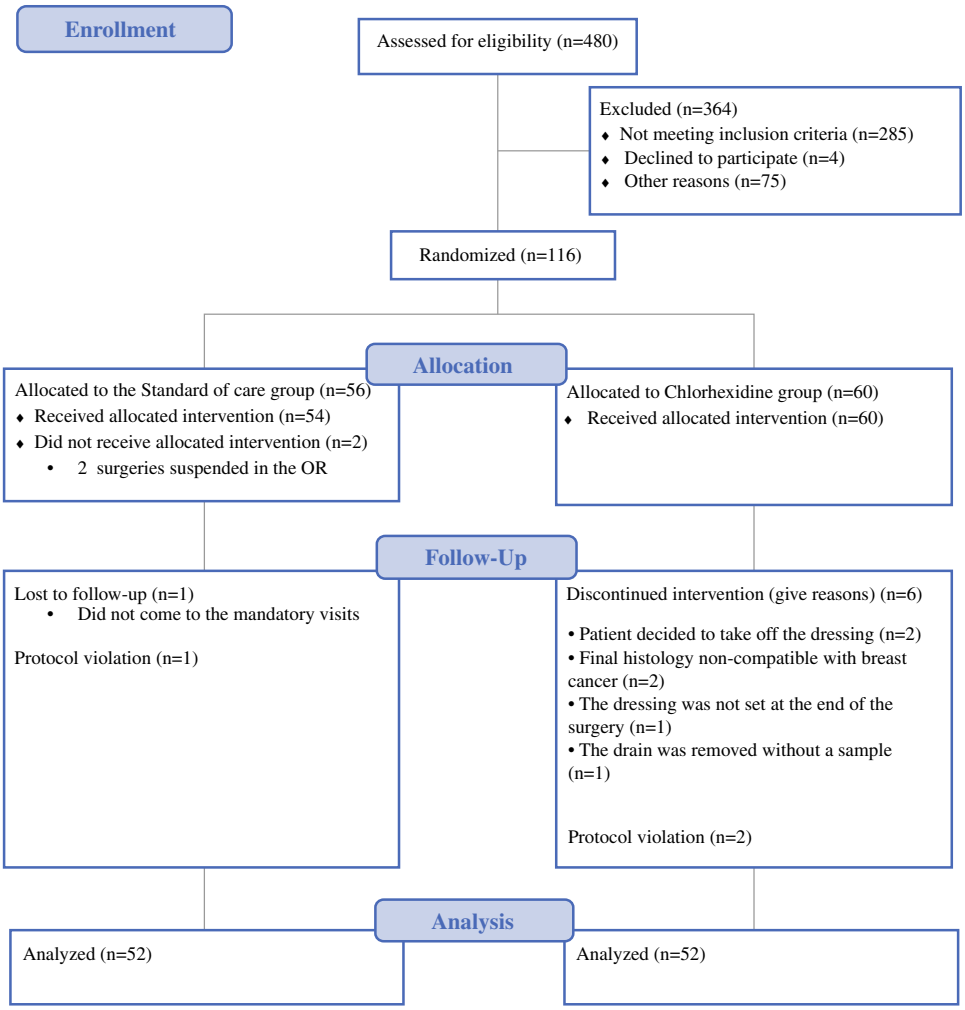

FIG. 1 Patients' flow diagram

differences between the two groups. Among the study patients, 41 (39.4%) were overweight, 30 (28.8%) were obese, and 71 (68.26%) had locally advanced breast cancer at diagnosis, with no differences between the groups. Detailed information on oncologic- and surgical-related variables are shown in Table 1.

Modified radical mastectomy was performed for 30 patients (55.6%) in the control group and 28 patients (52.8%) in the chlorhexidine group. Total mastectomy, with or without sentinel node biopsy, was performed for 12 patients (22.2%) in the control group and 14 patients (26.4%) in the chlorhexidine group. The BCS procedure, with or without ALND, was performed for 12 patients (22.2%) in the control group and 11 patients (20.8%) in the chlorhexidine group. Seven patients had IRTE, five (9.2%) in the control group and two (3.7%) in the chlorhexidine group ($p = 0.24$).

The median drain duration was 15 days in both groups ($p = 0.3$). An SSI developed for 11 patients, 8 (15.4%) in the control group and 3 patients (5.7%) in the chlorhexidine group ($p = 0.11$). A surgical-site complication developed for 17 patients (32.7%) in the control group and 15 patients (28.8%) in the antisepsis group ($p = 0.67$). Seroma, hematoma, flap necrosis, and wound dehiscence occurred in a similar proportion (Table 2).

Nine patients with an SSI were cultured. In six cases (66.6%), the pathogen in the fluid samples and in the drain tip were the same as that found in the infected wound. Details on the infected patients are described in the Supplementary Material (Table S1).

Bulb fluid cultures at POW 1 were positive for 39 (42.9%) of the control group compared with 22 (28.9%) of the chlorhexidine group ($p = 0.06$) (Fig. 2). Cultures from the POW 2 assessment were positive for 54 (79.4%) of the control group versus 39 (54.9%) of the chlorhexidine group ($p = 0.001$). Cultures from drain tubes were positive for 67 (79.8%) of the control group and 37 (50.7%) of the chlorhexidine group ($p = < 0.001$; Fig. 2).

Bacterial isolations are depicted in Table 3. At POW 1, 49 pathogens were isolated from the control-group versus 36 from the chlorhexidine group. *Staphylococcus* spp was

TABLE 1 Clinical and demographic characteristics

	Control (n = 52) n (%)	Antisepsis (n = 52) n (%)	p value
Mean age (years)	52 ± 12	55 ± 13	0.30
BMI			
Normal	15 (28.8)	18 (34.6)	0.733
Overweight	21 (40.4)	20 (38.5)	
Obesity	16 (30.8)	14 (26.9)	
Current smoking	9 (17.3)	9 (17.3)	1.000
Diabetes mellitus	9 (17.3)	10 (19.2)	0.800
Clinical stage			
In situ	0	3 (5.8)	
Localized	16 (30.7)	11 (21.15)	
Locally advanced	33 (63.4)	38 (73.07)	0.198
Metastasized	3 (5.8)	0	
Histology			
Ductal	40 (76.4)	39 (75.0)	
Lobular	4 (7.7)	8 (15.4)	0.298
Papillary	0	1 (1.9)	
Mixed	8 (15.4)	4 (7.7)	
Neoadjuvant therapy			
None	27 (51.9)	26 (50)	
Chemotherapy	25 (48.1)	26 (50)	0.844
Trastuzumab	10 (19.2)	10 (19.2)	1.000
ASA class			
1	27 (51.9)	32 (61.5)	0.596
2	23 (44.2)	18 (34.6)	
3	2 (3.8)	2 (3.8)	
Procedures[a]			
Radical	42 (77.8)	42 (79.2)	1.00
BCS with/ or without ALND	12 (22.2)	11 (20.8)	
Bilateral procedures	2 (3.8)	1 (1.9)	1.00
Median surgery duration: min (IQR)	130 (108–175)	130 (106–163)	0.304
Median surgery bleeding: ml (IQR)	100 (50–150)	100 (50–150)	0.882
Transfusion	1 (1.85)	1 (1.88)	1.00
No. of drains (n = 167)[b]	86 (51.5)	81 (48.5)	
Median drain duration: days (IQR)	15.5 (12.5–19.25)	15 (13–20.25)	0.53
Median 24-h drain volume: ml (IQR)	50 (30–50)	50 (33–73)	0.14
POW 1	30 (20–37.5)	25 (20–35)	0.81
POW 2			

BMI, body mass index; ASA, American Society of Anesthesiologists; BCS, breast-conserving surgery with/ or without ALND (axillary lymph node dissection); IQR, interquartile range; POW, postoperative week

[a]The number of surgical procedures exceeds the number of patients because one patient can have a bilateral surgery

[b]The number of drains exceeds the number of patients because one patient can have more than one drain

the most common specie in both groups. At POW 2, 97 pathogens were identified in the control group versus 70 pathogens in the chlorhexidine group.

Two adverse effects were reported, one related to the adhesive of the CHG dressing and one related to blisters that developed in the area covered by the CHG pad. No major adverse effects were reported. Both patients were treated with local care and showed full recovery.

TABLE 2 Surgical-site complications[a]

	Control (n = 52) n (%)	Antisepsis (n = 52) n (%)	p value
Seroma	13	9	0.11
Hematoma	2	1	1.0
Partial flap necrosis[b]	4	4	1.0
Wound dehiscence	3	4	1.0
Fat necrosis	0	1	–
SSI[a]	8 (15.4)	3 (5.8)	0.11
Radical	8 (15.4)	3 (5.8)	0.11
BCS with/ or without ALND	0	0	0

SSI, surgical-site infection; BCS, breast-conserving surgery with/ or without ALND (axillary lymph node dissection)

[a]One patient from the control group with radical mastectomy and immediate reconstruction with tissue expander experienced an SSI

[b]Three patients from the antisepsis group experienced skin radiation injury over the flap while in radiation therapy

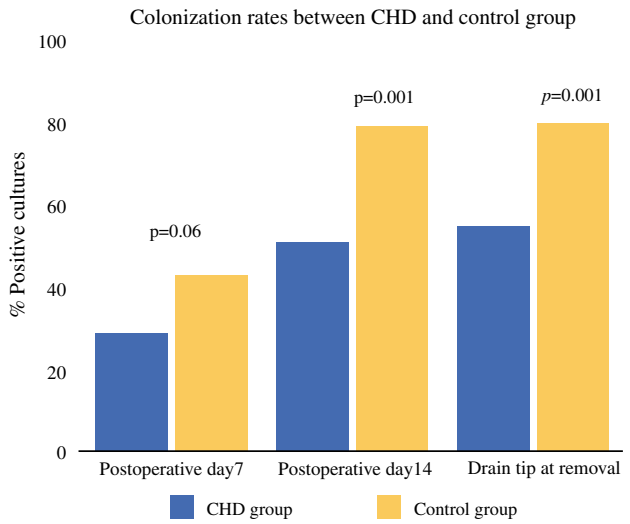

FIG. 2 Colonizaton rates between CHD and control group, in the bulb fluid at the 7th and 14th postoperative day (POD); and in the drain tube at removal

We evaluated the use of a quantitative real-time PCR aimed at the *16S rRNA* gene to quantify the bacterial load in fluid samples and drain tips. We processed 167 samples at the end of POW 1 and 139 samples at the end of POW 2. Medians and interquartile ranges (IQRs) and cutoff points are shown in Figure 1S in the Supplementary Material.

DISCUSSION

This study investigated the rate and bacterial load of drain colonization in patients undergoing breast cancer surgery using chlorhexidine-impregnated dressings at the drain exit site. We found that the use of chlorhexidine dressings significantly reduced the bacterial colonization of the drainage system.

In our setting, surgical drains remain in situ for prolonged periods in breast surgery, up to 3 weeks. Chlorhexidine dressings have been tested as a strategy for SSI reduction.

Two previous studies in breast surgery by Degnim et al.[17,18] evaluated the use of chlorhexidine sponges (Biopatch; Johnson & Johnson) and sodium hypochlorite in the drain bulb and showed a significant reduction in the colonization rates and fewer SSIs. Similar to the studies by Degmin et al.[17,18] the current study showed that chlorhexidine dressings decreased the rate of colonization and reduced the rate of SSI by one half (p = 0.1). In contrast to the former studies, we did not use a sponge. However, we did use a semi-permeable transparent dressing with a slow-release chlorhexidine-impregnated pad at the drain exit site. In addition to the antisepsis, we found that drains were better kept in place and had less kinking compared with the standard gauze dressing.

More recently, one study used chlorhexidine dressings (3M® Tegaderm® CHG) in external ventricular drains, with a decrease in the incidence of colonized catheters and infections, similar to our results.[20] Also, a study in epidural and peripheral regional catheters with the use of chlorhexidine-impregnated dressings found a significant reduction in colonization of the insertion sites and catheter tips. However, no reductions in rates of local infections were seen.[21]

The frequency of SSI at our institution for breast cancer surgery is higher than that reported in other series.[5–9] In our trial, the SSI rates were 50% lower in the intervention group, although this difference was not statistically significant because the sample was not powered to detect this difference. The low cost of the intervention and the safety of the dressing should be considered as an additional

TABLE 3 Microorganisms isolated in drainage culture

Pathogens	Control (n = 284) n (%)	Antisepsis (n = 164) n (%)
7 ± 1 PODs	49[a]	36[a]
Staphylococcus aureus	15 (30.6)	2 (5.6)
Coagulase-negative staphylococci	11 (22.4)	6 (16.7)
Enterococcus spp	8 (16.3)	5 (13.9)
Other GPC	0	1 (2.8)
Pseudomonas spp	3 (6.1)	5 (13.9)
Other nonfermenting GNB	5 (10.2)	5 (13.9)
Escherichia coli	0	0
Klebsiella spp	1 (2.1)	0
Enterobacter spp	2 (4.1)	5 (13.9)
Other fermenting GNB	3 (6.1)	1 (2.8)
Corynebacterium spp	0	2 (5.6)
Other GPB	1 (2.1)	2 (5.6)
Fungi	0	1 (2.8)
Anaerobic bacteria	0	1 (2.8)
14 ± 1 PODs	97[a]	70[a]
Staphylococcus aureus	19 (19.6)	3 (4.3)
Coagulase-negative staphylococci	16 (16.5)	19 (27.1)
Enterococcus spp	11 (11.3)	5 (7.1)
Other GPC	1 (1)	0
Pseudomonas spp	7 (7.2)	6 (8.6)
Other nonfermenting GNB	14 (14.4)	17 (24.3)
Escherichia coli	3 (3)	1 (1.4)
Klebsiella spp	2 (2)	2 (2.9)
Enterobacter spp	5 (5.1)	8 (11.4)
Other fermenting GNB	6 (6.2)	1 (1.4)
Corynebacterium spp	6 (6.2)	3 (4.3)
Other GPB	2 (1)	0
Fungi	3 (3)	3 (4.3)
Anaerobic bacteria	2 (2)	2 (2.9)
Drain tip	138[a]	58[a]
Staphylococcus aureus	29 (21)	6 (10.3)
Coagulase-negative staphylococci	62 (45)	26 (44.8)
Enterococcus spp	3 (2.2)	2 (3.4)
Pseudomonas spp	5 (3.6)	1 (1.7)
Other nonfermenting GNB	5 (3.6)	5 (8.6)
Escherichia coli	3 (2.2)	2 (3.4)
Klebsiella spp	2 (1.4)	3 (5.2)
Enterobacter spp	1 (0.7)	8 (13.8)
Other fermenting GNB	2 (1.4)	0
Corynebacterium spp	20 (14.5)	3 (5.2)
Other GPB	4 (2.9)	0
Fungi	1 (0.7)	2 (3.4)

POD, postoperative day; GPC, Gram-positive cocci; GNB, Gram-negative bacilli; GPB, Gram-positive bacilli

[a]Total number of bacteria is different for each sampling moment. One sample could have more than one isolation. Percentages were calculated for the total of pathogens per day of sampling

preventive tool for SSI in breast surgery. Other surgical-related complications were observed in a similar proportion in both groups.

Staphylococcus aureus and *Staphylococcus coagulase-negative* were the most frequently isolated microorganisms. Although Gram-positive cocci were the predominant agents, Gram-negative bacilli were found in about 50% of the cases. *Enterococcus* spp and *Pseudomonas* spp were observed more frequently in fluid samples from the control group compared with the antiseptic group. This finding supports the theory of possible contamination from the external environment via the drainage system and warrants more attention.[22,23]

Breast microbiota has been studied recently because of its association with cancer and other diseases. A few studies have characterized tissue microbiota and found a predominance of *Proteobacteria*, *Firmicutes*, *Bacteroidetes*, and *Actinobacteria.*[24–26] Although the relationship between these microorganisms and diseases is not clear, the breast has its own microbiota, and it changes under specific circumstances. This diversity could explain drain colonization and SSI.

After POW 2, nearly 80% of the drains were colonized. Most of the SSIs occurred between POWs 2 and 3, consistent with the increased risk of SSI reported in other series.[6,15,27] This information also emphasizes the importance of prompt drain removal, which does not always depend on low fluid volumes as recommended, but also depends on surgeons' preferences and other nonmedical aspects (e.g., administrative issues). The use of CHG-impregnated dressings also might help to diminish the risk of infection in scenarios of drain care at the patient's home that are not clear or situations in which unknown sanitation conditions prevail.

A novel approach of our study comprised the microbiology analysis because no recommendations exist on drain fluid analysis or best microbiological techniques. We used the semi-quantitative roll-plate culture as the gold standard based on evidence obtained from central venous catheter cultures, but we also used quantitative real-time PCR *16S* gene analysis for a more precise measurement of bacterial load.[28–30]

Our study had some limitations. We were unable to evaluate antimicrobial susceptibility or chlorhexidine resistance, which has been linked to the use of this antiseptic. Due to the nature of the study, blinding was not possible, neither for the investigators nor for the surgeons, and although the latter did not know the patients' allocation until the end of the procedure, some biases may have been introduced. Although fewer infections occurred in the intervention group, the trial lacked statistical power to detect SSI differences. Despite the these limitations, because breast cancer surgery is highly standardized, the chance of confounding was probably low.

In summary, the use of chlorhexidine gluconate-coated dressings on the skin of the drain exit site decreased the rate of bacterial colonization, with greater differences between the groups at POW 2. Fluid-isolated microorganisms correlated with those found on the drain tip and those from SSI.

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DISCLOSURE 3M donated the Chlorhexidine-coated dressing (Tegaderm CHG; 3M) and was not involved in the writing of the research protocol, in the performance of the study, or in the analysis of the results. The authors declare no conflicts of interest related to this manuscript.

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