

Povidone-iodine Does Not Affect Acellular Dermal Matrix Integration in Patients Undergoing 2-staged, Prepectoral, Breast Reconstructive Surgery

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Background: Povidone-iodine has been traditionally used as an antimicrobial agent to irrigate the breast pocket and rinse the prosthesis before placement in the pocket. Use of povidone-iodine with breast implants was banned from 2000 to 2017. During this period, acellular dermal matrix (ADM) was introduced to breast surgery. In nonclinical studies, povidone-iodine can impair collagen synthesis and kill fibroblasts. Cellular repopulation was critical for ADM integration. Whether povidone-iodine impacts ADM integration was unknown.

Methods: Patients who underwent immediate, prepectoral, 2-staged breast reconstruction were included in this retrospective study. Study population was divided into povidone-iodine-treated patients and triple-antibiotic-treated patients. The breast pockets were rinsed with the antimicrobial agent, and the prostheses and ADMs were presoaked in the agent perioperatively. At implant exchange, the extent of ADM integration was clinically assessed. ADM integration was defined as >25% of matrix vascularization. ADM integration and postoperative complications were compared between the groups.

Results: A total of 111 patients (257 reconstructions) were included—58 patients (111 reconstructions) were exposed to povidone-iodine and 53 patients (97 reconstructions) to triple-antibiotic solution. ADM integration was noted in 97% of breasts in each group. Integrated matrices appeared healthy, had no signs of foreign body reaction, and demonstrated punctate bleeding. Complications did not differ between the groups, including the rate of infections, seroma, and expander loss.

Conclusion: Irrigation of the breast pocket and presoaking of the prosthesis and ADM with povidone-iodine appear to have no adverse consequences on clinical outcomes and did not impede matrix integration. (*Plast Reconstr Surg Glob Open* 2020;8:e2758; doi: [10.1097/GOX.0000000000002758](https://doi.org/10.1097/GOX.0000000000002758); Published online 23 April 2020.)

INTRODUCTION

Povidone-iodine is an antimicrobial agent that has been used for decades for antisepsis and wound healing applications. It has many favorable attributes, including

a broad spectrum of antimicrobial activity, ability to penetrate biofilms, lack of resistance, anti-inflammatory properties, low cytotoxicity, good tolerability, and no negative effect on wound healing.^{1,2}

In breast surgery, povidone-iodine has been traditionally used as an antiseptic agent to irrigate the breast pocket and rinse the prosthesis before placement in the pocket. In 2000, the US Food and Drug Administration banned the use of povidone-iodine with breast implants due to concerns regarding adverse effect on shell integrity that could potentially lead to implant deflation or rupture.³ The ban was based on 2 studies: one reporting valve patch delamination from long-term intraluminal

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povidone-iodine fill of saline implants⁴ and the other reporting changes in elastomer strength and color from soaking the fill tube, rather than the implant shell (which was manufactured differently), in povidone-iodine.⁵ In both studies, povidone-iodine was not used for pocket irrigation as was the practice in breast surgery. The Food and Drug Administration subsequently lifted the ban in the fourth quarter of 2017 in response to a breast implant manufacturer's request.²

To date, there has been no study that has demonstrated unequivocally that povidone-iodine compromises breast implants or tissue expanders. Similarly, no human study has shown povidone-iodine to be cytotoxic or inhibit wound healing.¹ But data from animal and in vitro studies indicate that povidone-iodine can impair collagen synthesis, have a toxic effect on fibroblasts and keratinocytes, and impair epithelial cell migration.^{6,7} The cytotoxic effects of povidone-iodine, albeit from nonhuman studies, are concerning because acellular dermal matrix (ADM) is frequently used in prosthetic breast reconstruction.⁸ Cellular (fibroblasts) repopulation and infiltration are critical steps in matrix viability and its integration into host tissue.^{9–12} Povidone-iodine could, thus, potentially impede the integration of the ADM. The impact of povidone-iodine on ADM integration has not yet been assessed and is the focus of this retrospective study.

PATIENTS AND METHODS

Study Population

Consecutive patients who underwent immediate, prepectoral, 2-stage (expander/implant), breast reconstruction following mastectomy between August 2016 and March 2018 in the author's (A.G.) practice were included in this retrospective study. Patients who underwent delayed reconstruction, revision reconstruction, and hybrid (autologous/prosthetic) procedures were excluded from the study. Patients at risk of infectious complications such as those who had neoadjuvant or adjuvant therapy and those who did not receive negative pressure wound therapy were also excluded from the study. The study population was segregated into those who had received triple-antibiotic rinse (between August 2016 and April 2017) and those who had received povidone-iodine rinse (between May 2017 and March 2018) during surgery. This study was approved by the PeaceHealth Southwest Medical Center Institutional Review Board (Vancouver, Wash.).

Reconstructive Surgery

Immediate, prepectoral, expander/implant, breast reconstruction was performed as previously described.¹³ Following skin-sparing mastectomy, nipple-sparing mastectomy, or skin-reducing mastectomy, the prepectoral pocket was collapsed and adjusted as needed to accommodate the selected expander.

In patients who received povidone-iodine, the expander and ADMs [a 16 × 20 cm sheet of AlloDerm SELECT Regenerative Tissue Matrix and a sheet of large Contour (10.7 × 21.5 cm) Artia Reconstructive Tissue

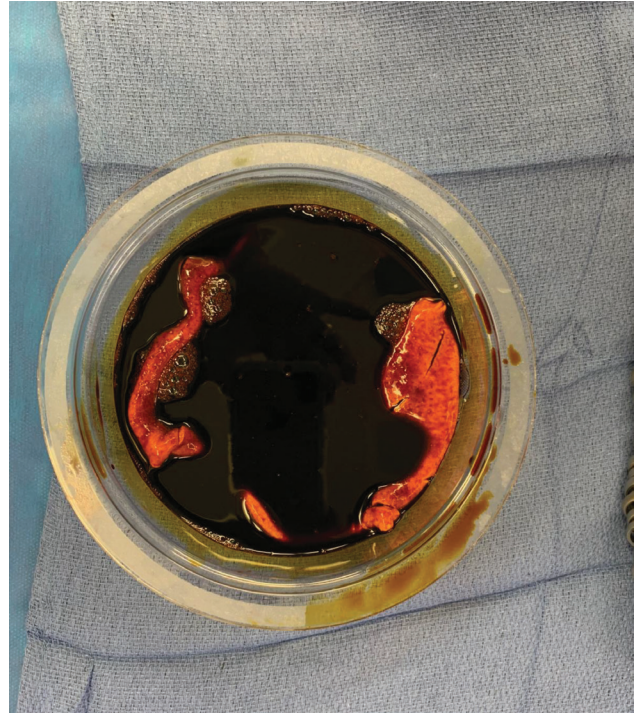


Fig. 1. Acellular dermal matrices presoaked in full-strength povidone-iodine solution.

Matrix (Allergan Plc, Bridgewater, N.J.)] were presoaked in full-strength povidone-iodine solution (10%) for 10–40 minutes (Fig. 1) while waiting for the completion of the mastectomy. The prepectoral pocket was rinsed with 500 mL of half-strength (5%) povidone-iodine plus bacitracin (50,000 IU). In patients who received triple-antibiotic solution, the expander and ADMs were presoaked in a solution containing 1 g of cefazolin, 80 mg of gentamicin, and 50,000 IU of bacitracin in 1 L normal saline for 10–40 minutes as above. The prepectoral pocket was rinsed with 500 mL of the same triple-antibiotic solution.

Before its insertion, the upper portion of the expander was wrapped with AlloDerm and the lower portion with Artia (Fig. 2). The wrapped expander was placed in the prepectoral pocket and secured to the pectoralis major muscle and subcutaneous tissues. Two drains were placed in each breast, between the matrices and the mastectomy flap, and the incision was closed in layers. The expander was inflated with saline to 50%–70% of capacity. A closed-incision negative pressure therapy (PREVENA Incision Management System; KCI, San Antonio, Tex.) was applied to the incision and nipple-areolar complex (if nipple-sparing), to cover and protect the incision from contamination. Implant exchange was performed approximately 3 months after initial surgery.

Data Collection and Analyses

All complications, including surgical-site infection, skin necrosis, seroma, prosthesis exposure or loss, return to operating room, and capsular contracture that occurred from expander placement to implant exchange, were retrieved from patient records. At implant exchange, the extent of ADM integration was clinically assessed by

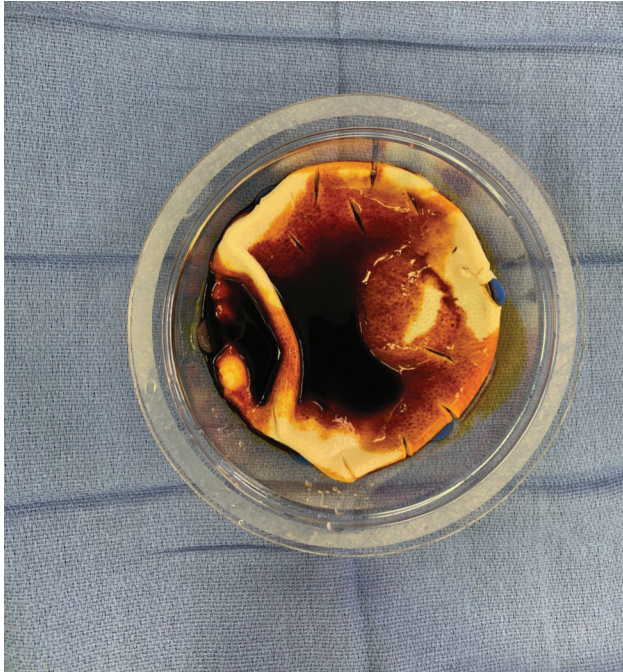


Fig. 2. Expander-matrix construct.

estimating the percentage of vascularization noted on the surface of the matrix. ADM integration was defined as >25% of matrix vascularization while failed incorporation was defined as <25% vascularization of the matrix. To assess the proportion of matrix integration or nonintegration, we divided the anterior and posterior surfaces into quadrants and clinically assessed for vascularization. If >25% of the surface of the matrix appeared to be unincorporated, that is, nonadherent or free floating, the matrix was completely removed during implant exchange. Basic demographic data (age and body mass index), comorbidities (smoking status, obesity, diabetes, and hypertension), and type of mastectomy were also retrieved from patient records. Retrieved data were compared between the 2 groups—povidone-iodine group and triple-antibiotic group. Statistical differences between groups were assessed using the Fisher's exact test for categorical variables and Student's *t* test for continuous variables, setting the significance level at below 5%.

RESULTS

A hundred eleven patients (257 reconstructions) met the inclusion criteria and were analyzed in this study. Fifty-eight of the patients (111 reconstructions) were exposed to povidone-iodine and 53 patients (97 reconstructions) were exposed to triple-antibiotic solution (Table 1). Both groups of patients were well matched in baseline characteristics with no significant difference in demographics and comorbidities. The only significant difference was seen in the type of mastectomy. Patients exposed to triple-antibiotic solution had a higher rate of skin-reducing mastectomy. Rates of skin-sparing mastectomy and nipple-sparing mastectomy were not significantly different between the groups.

Table 1. Baseline Patient and Procedural Variables

Variables	Povidone-iodine Group	Triple-antibiotic Group	<i>P</i>
No. patients	58	53	NA
No. breasts	111	97	NA
Laterality, no. patients (%)			0.254
Unilateral	5 (8.6)	9 (17.0)	
Bilateral	53 (91.4)	44 (83.0)	
Age (y), mean ± SD (range)	51.98 ± 11.40 (31–77)	52.95 ± 12.73 (34–77)	0.746
BMI (kg/m ²), mean ± SD (range)	30.12 ± 8.00 (18–62)	28.65 ± 6.5 (17–44)	0.268
Comorbidity, no. patients (%)			
Smoker	0 (0.0)	2 (3.8)	0.226
Diabetes	15 (25.9)	13 (24.5)	1.000
Obesity	28 (48.3)	18 (34.0)	0.177
Hypertension	15 (25.9)	21 (73.6)	0.156
Mastectomy, no. breasts (%)			
SSM	37 (33.3)	28 (28.9)	0.550
NSM	47 (42.3)	28 (28.9)	0.060
RSM	27 (24.3)	41 (42.3)	0.008*

*Statistically significant.

BMI, body mass index; NA, not applicable; NSM, nipple-sparing mastectomy; RSM, reduction-pattern, skin-sparing mastectomy; SSM, skin-sparing mastectomy.

Table 2. Complications after First-stage Expander Placement

Complication	Povidone-iodine Group	Triple-antibiotic Group	<i>P</i>
	No. Breasts = 111 n (%)	No. Breasts = 97 n (%)	
Skin necrosis	10 (9.0)	11 (11.3)	0.648
Major	5 (4.5)	6 (6.2)	0.758
Seroma	0 (0.0)	3 (3.1)	0.100
SSI	1 (0.9)	4 (4.1)	0.187
Major	1 (0.9)	4 (4.1)	0.187
Wound dehiscence	5 (4.5)	7 (7.2)	0.553
Expander exposure	3 (2.7)	3 (3.1)	1.000
Return to OR	3 (2.7)	6 (6.2)	0.309
Expander loss	2 (1.8)	1 (1.0)	1.000
Capsular contracture	0 (0.0)	0 (0.0)	1.000
Any complication	10 (9.0)	14 (14.4)	0.278

OR, operating room; SSI, surgical-site infection.

During the period from first-stage, expander reconstruction to second-stage implant exchange, complications occurred in 24 breasts (9.3%), of which 10 breasts (9.0%) were exposed to povidone-iodine and 14 breasts (14.4%) to triple-antibiotic solution (Table 2). Complications related to the use of antiseptic solution, such as surgical-site infection (0.9% versus 4.1%), seroma (0% versus 3.1%), and expander loss (1.8% versus 1.0%), did not differ significantly between the povidone-iodine and triple-antibiotic groups. Seroma was diagnosed clinically when patients complained of pain and swelling and was resolved by drainage. Other complications such as skin necrosis (9.0% versus 11.3%), wound dehiscence (4.5% versus 7.2%), and expander exposure (2.7% versus 3.1%) also did not differ among the groups (povidone-iodine versus triple-antibiotic solution, respectively).

At implant exchange, ADM integration (ie, >25% of the matrix surface was integrated) was noted in 97% of breasts

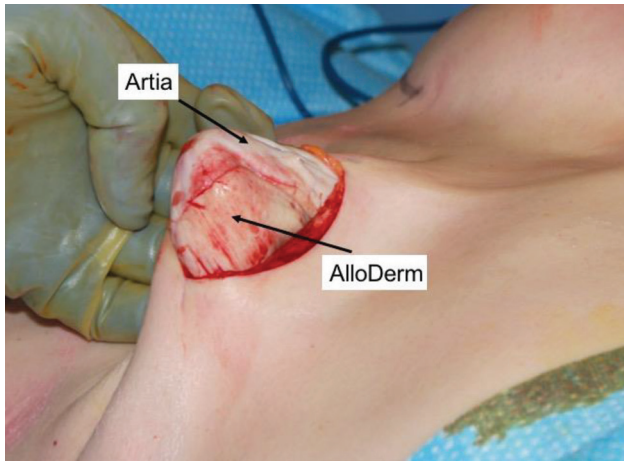


Fig. 3. Integrated acellular dermal matrices (Artia and AlloDerm).

in each group. Grossly, integrated matrices appeared healthy, had no signs of foreign body reaction (encapsulation, resorption, or contracture), and demonstrated punctate bleeding (Fig. 3). However, none of the matrices were 100% integrated. In all of the cases, there were some areas of nonadherence at the superior edge, lateral edge, or axillary tail due to the technical difficulty of attaining a smoothed surface in these areas. The nonadherent areas of the matrix were exercised, and the capsule that had formed under the matrix was cauterized (popcorn capsulorrhaphy). In 3 breasts (2.7%) exposed to povidone-iodine and 3 breasts (3.1%) exposed to triple-antibiotic solution, the ADMs were found to be unincorporated (ie, >25% of the matrix was unincorporated). The unincorporated areas were “free floating,” that is, were nonadherent to the overlying mastectomy flap or underlying chest wall. Unincorporated ADMs were completely removed. No additional ADM was utilized at the second stage. Povidone-iodine-soaked implant was then placed into the pocket.

After second-stage implant exchange, all patients had an uneventful clinical course without any significant complications requiring reoperation. There was also no incidence of capsular contracture during a follow-up period of 21.3 ± 5.5 months (range, 11.4–31.3 months).

DISCUSSION

Povidone-iodine is iodine complexed with the synthetic carrier polymer povidone.¹ Iodine is the active component of the complex; povidone is inert and has no antimicrobial activity. Iodine’s microcidal prowess has been known for over a century and half and there is extensive experience with its use as an antiseptic and in wound healing. In breast surgery, povidone-iodine is used intraoperatively to eliminate microbial contaminants from the breast pocket and the surface of expanders and implants and mitigate surgical-site infection, capsular contracture, and breast-implant-associated anaplastic large-cell lymphoma.^{14,15} Povidone-iodine has a broad spectrum of activity and is effective against a variety of bacterial strains, both Gram-negative and Gram-positive, including methicillin-resistant *Staphylococcus aureus* and *Ralstonia pickettii*

(linked to breast-implant-associated anaplastic large-cell lymphoma), and bacterial biofilms (linked to capsular contracture).¹

Since the introduction of ADM in breast reconstruction in 2004, ADM has become an integral part of prosthetic breast reconstruction, particularly in prepectoral reconstruction. Currently, 75% of prosthetic breast reconstructions in the United States include an ADM for prosthesis and soft tissue support.⁸ With the reintroduction of povidone-iodine in breast surgery in 2017, there have been concerns regarding the potential cytotoxicity of povidone-iodine on ADM based on findings from animal and in vitro studies. In these nonclinical studies, full- or half-strength povidone-iodine impaired collagen synthesis and killed fibroblasts and keratinocytes.^{6,7}

In this clinical study, the authors have shown that presoaking of the ADMs in full-strength povidone-iodine did not affect the subsequent incorporation of the matrices into host tissue. Adequate cellular repopulation (including fibroblasts) and neovascularization of ADM are required for its integration into host tissue.^{9–12} Based on the observed integration of over 97% of grafts exposed to povidone-iodine in this study, one can conclude that povidone-iodine was neither cytotoxic nor adversely affected matrix integration.

This study also demonstrated that triple-antibiotic rinse is an effective alternative to povidone-iodine for mitigating surgical-site infection and associated complications of seroma and prosthesis loss. Previous studies have shown a lower rate of capsular contracture with povidone-iodine (<2.5%),^{14,15} with one study reporting a 10-fold lower rate with povidone-iodine breast pocket irrigation versus single perioperative dose of intravenous cephalothin followed by postoperative oral cephalexin for 7 days.¹⁴ In the present study, capsular contracture was not observed, both in the triple-antibiotic and in the povidone-iodine group. A likely explanation is the role played by ADM in mitigating the risk of capsular contracture by inhibiting the inflammatory and profibrotic signaling that causes capsule formation.^{16–19} The authors have consistently observed an extremely low rate of capsular contracture in over 700 prepectoral reconstructions (<1.0%) where the prosthesis was completely wrapped or anteriorly covered with ADM.^{20–22}

There are several limitations to this study; the most significant of which is the lack of histologic evidence of graft integration. Although grossly and clinically povidone-iodine did not appear to have any effect on graft integration, from an academic standpoint, it would have been interesting to see the effect, if any, on fibroblast repopulation of the matrices. Other limitations include the retrospective nature of the study and the lack of objective quantification of matrix integration. Notwithstanding these limitations, irrigation of the breast pocket with povidone-iodine or presoaking of the expander and ADMs with povidone-iodine appear to have no adverse consequences on graft integration or clinical outcomes.

CONCLUSIONS

Povidone-iodine does not appear to exert cytotoxic effects or impede the integration of ADM used for prosthesis coverage and support in prepectoral breast reconstruction. The perioperative antiseptic procedure of irrigating the breast pocket and presoaking the ADM and prosthesis with povidone-iodine to remove surface bacteria is a safe procedure.

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