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The new bioabsorbable sheet for the sling method in immediate breast reconstruction with expander-implant: a study protocol for interventional prospective study

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ABSTRACT

The popularity of a sling method using biomaterial sheets for immediate breast reconstruction based on prosthesis has been increasing in western countries. However, acellular dermal matrix, which is representative of the biomaterial sheet, is not available and the sling method also has not been accepted in Japan. We focused on a new bioabsorbable sheet (NEOVEIL sheet) as a substitute for the sling method and report a prospective study protocol to assess the safety and effectiveness of this material. This was an ongoing, single center, open-label, single-arm study. Inclusion criteria and exclusion criteria are defined restrictively. If the surgeon determined that the perfusion of skin envelope after mastectomy is poor, the surgical procedure can be modified and that patient was excluded from the study. The primary outcome was the incidence of tissue expansion or implant explantation occurring within 1 month after surgery. The secondary outcomes are as follows: (1) aesthetic outcome using a rating scale; (2) symmetry of the nipple areolar complex position; (3) patient reported outcomes using BREAST-Q; (4) pain intensity using the Visual Analog Scale; (5) histology of the capsule around the tissue expander; (6) inflation volume at the first stage and overall inflation time of expansion; and (7) other adverse events regarding the surgery. This study will determine the safety and effectiveness of the sling method using a NEOVEIL sheet in Japanese women.

Keywords: sling method, immediate breast reconstruction, tissue expander, biomaterial, prospective study

Abbreviations:
TE: tissue expander
ADM: acellular dermal matrix

INTRODUCTION

Immediate breast reconstruction based on tissue expander (TE) and implant has been the most popular breast reconstruction procedure. To reduce the risk of TE/implant exposure due to poor skin perfusion following mastectomy, the TE/implant is inserted beneath the pectoralis

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major muscle and is then covered with muscle, especially in the upper pole with fascia or the serratus anterior muscle during the first stage in the conventional method.[1] This muscular pocket method has some disadvantages such as a limitation of the first expansion volume, repeated expansion after surgery, and stiffness in the lower pole due to muscle and fascia tension causing an unnatural shape in the lower pole. Currently, a sling method using an acellular dermal matrix (ADM) or another bioabsorbable synthetic sheet for immediate breast reconstruction based on the prosthesis has been gaining popularity in western countries.[2,3] In the sling method, these biomaterial sheets cover the lower lateral pole of the TE/implant to create a larger submuscular pocket and a natural breast shape. Furthermore, in cases of good skin viability, a direct implant can be performed using this technique.[4,5] However, ADM is not available and the sling method has not been accepted in Japan. Moreover, there remains considerable controversy about the safety of this procedure because of a possibility of increased complications, such as seroma, infection, and more frequent explantation, compared with the conventional submuscular pocket method.[6,7] On the other hand, the synthetic biomaterial sheet has some advantages that it is easily available in Japan and is not very expensive compared with ADM. Some reports about the sling method using synthetic biomaterial sheets have suggested about its safety and cost effectiveness, but there are only few studies with a high level of evidence.[8-10]

We focused on bioabsorbable polyglycolic acid felt (NEOVEIL sheet; GUNZE medical division, Japan) as an alternative to the sling method. The NEOVEIL sheet has some advantages compared with the ADM. The sheet is relatively inexpensive and available in Japan; furthermore, it has already been used to reinforce surgical suture stitches or prevent air leakage in thoracic surgery for several decades with a low complication profile.[11,12] We report a prospective study to assess the safety and effectiveness of the NEOVEIL sheet in immediate two-stage breast reconstruction based on TE with the sling method.

METHODS

Trial Design

This is a single center, open-label, single-arm study. The study was approved by the ethical committee of Okayama University Hospital and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Registration of the study participants began in February 17, 2015. We are currently following up and investigating the participants. The study was registered in the University Hospital Medical Information Network Center (UMIN)-Clinical Trials Registry on August 11, 2015 (UMIN000018644). The study's design is shown in Fig. 1.

Eligibility Criteria

Inclusion criteria: (1) patients with primary breast cancer who were planning to undergo bilateral or unilateral mastectomy and immediate breast reconstruction with tissue expander; (2) age ≥20 years old at registration; (3) a body mass index of ≤25 kg/m^2; (4) patients who had no severe ptosis defined as less than grade 3 in the Regnault classification[13]; (5) those who were not active smokers; (6) patients who received a full explanation of the study from an investigator or sub-investigator at an institution in the study via an informed consent form.

Exclusion criteria: (1) inflammatory breast cancer; (2) patients who received prior radiation therapy on the side of their breast who were planning to undergo breast reconstruction; (3) continuous administration of a steroid hormone or immunosuppressant for another disease; (4) those with active diabetes mellitus; (5) those with an active collagen disease; (6) those otherwise deemed unsuitable for the study by an investigator.

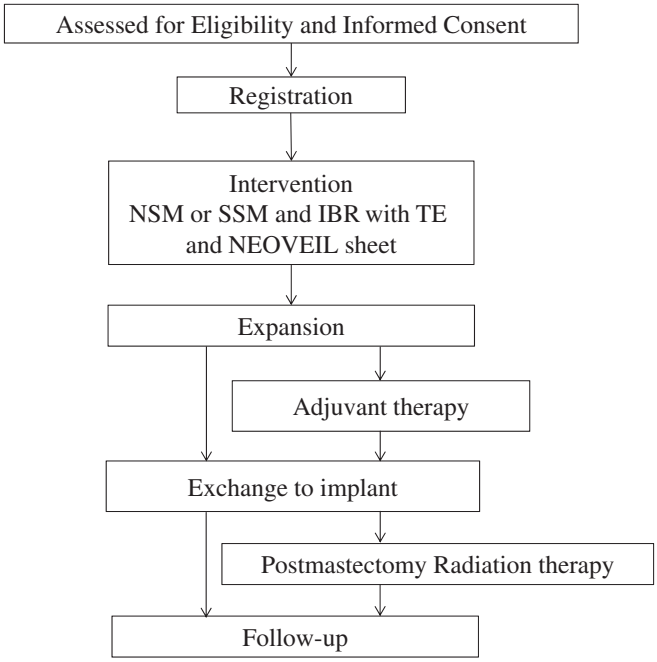

Fig. 1 Flowchart of the current trial
NSM: nipple sparing mastectomy, SSM: skin sparing mastectomy, IBR: immediate breast reconstruction, TE: tissue expander

Intervention

All patients underwent immediate breast reconstruction following nipple sparing or skin sparing mastectomy with expander during the first stage and exchange to a silicon implant within the second stage in another admission. In this study, during the first surgical stage, a tissue expander pocket was created under the pectoralis major after releasing the attachment of the muscle on the caudal side and a bioabsorbable polyglycolic acid felt (NEOVEIL sheet, GUNZE medical division, Japan) was sewn from the released area of the muscle to the inframammary fold to suspend the tissue expander on the lower pole of the breast. Any fascia or serratus muscle was not elevated, as in the standard submuscular pocket method. A NEOVEIL sheet was saturated within 15 weeks after implantation. The thickness and size of the sheet used in this study was 0.4 mm and 100 cm^2 respectively. Except for this procedure, surgical techniques of breast reconstruction with tissue expander and implant were performed in the same manner. If the surgeon determined that perfusion of the skin envelope was poor after mastectomy during the first-stage operation, this surgical procedure could be modified depending on the surgeon; these patients were dropped out from the study. The intraoperative expansion volume was evaluated by the postoperative treatment results, which included pain control, administration of prophylactic antibiotics, drainage management, and rehabilitation, which will be performed identical to the preoperative state in our institution. Expansion will begin in the outpatient clinic three weeks post-operatively and continue until a three-week interval.

Outcomes

The primary outcome of this study was the incidence of the tissue expander or implant

explantation that occurred within one month postoperatively as defined as a grade IIIb in the Clavien-Dindo classification.[14] The secondary outcomes were as follows: (1) aesthetic outcome using the rating scale according to photography; (2) symmetry of the nipple areolar complex position using the Mamma-balance technique[15]; (3) patient-reported outcome using the BREAST-Q[16]; (4) pain intensity using the Visual Analog Scale; (5) histology of the capsule around the tissue expander; (6) inflation volume at the first stage and overall inflation time of the expander; and (7) other safety assessments: any other adverse event regarding the surgery, except the primary outcome as shown in Table 1.

Data collection methods

Tables 2 and 3 show the timetable of intervention and data collection during the first and second stages, respectively. The investigators will maintain the clinical records for each patient as a source of data, including a copy of the informed consent, medical records, laboratory data, image data, patient diaries, and other records or notes. All data were collected by clinicians at the Okayama University Hospital. Clinical data entry and data management will be performed. An interim analysis will be performed after seven patients are enrolled in this study; auditing is planned. If any severe adverse events occurred, including the primary outcome during this study period, a data and safety monitoring committee will meet.

Statistical Considerations

Sample size. According to the historical study,[17-19] the required sample size was estimated based on a threshold incidence of complications of 15% and an expected incidence of complication of 2%, 80% power, and an alpha value of 0.05. Given the two dropout patients, the target sample size was determined to be at least 30 patients. If there were more than two patients with complications defined as the primary outcome, we considered this procedure not to be accepted widely.

Table 1 Surgical adverse event

Short-term complication within 1 month after surgery		
	Seroma*	(yes/no)
	Hematoma*	(yes/no)
	Infection†	(yes/no)
	Skin necrosis*	(yes/no)
	NAC necrosis*	(yes/no)
	Exposure of tissue expander or implant	(yes/no)
	Any other surgical complication	(yes/no)
Long-term complication		
	Infection†	(yes/no)
	Exposure of tissue expander or implant*	(yes/no)
	Rupture of implant*	(yes/no)
	NAC hypopigmentation	(yes/no)
	Any other surgical complication	(yes/no)

* GradeIIIb in the Clavien-Dindo classification
† GradeIIIa in the Clavien-Dindo classification
NAC: nipple areolar complex

Table 2 Timetable of intervention and data collection at first stage

	Preoperative research	1st stage Operation	Postoperative research			
	Baseline	NSM or SSM and IBR with TE using NEOVEIL sheet	1 week	1 month	· · ·	03 months
Follow-up			○	○	○	○
Patient background	○					
BREAST-Q	○			○		○
Photograph	○			○		○
3D scanner	○			○		○
VAS (pain)	○	○	○	○	○	○
Surgical adverse event		○	○	○	○	○

NSM: nipple sparing mastectomy, SSM: skin sparing mastectomy, IBR: immediate breast reconstruction
TE: tissue expander

Table 3 Timetable of intervention and data collection at second stage

	Preoperative research	2nd stage Operation	Postoperative research			
		Exchange to implant	1 month	3 months	6 months	12 months
Follow-up			○	○	○	○
Patient background	○					
Harvest of capsule tissue		○				
BREAST-Q	○		○	○	○	○
Photograph	○		○	○	○	○
3D scanner	○		○	○	○	○
Surgical adverse event	○	○	○	○	○	○

Statistical Analysis. Continuous variables were presented as mean±standard deviation, and categorical variables were presented as percentage (frequency). Historical control will be regarded as control group data because this study is a single-arm study. The Mann-Whitney test was applied for comparison of continuous variables and χ^2 test or Fisher's exact test for categorical variables, with a significance set at $p < 0.05$. Statistical analysis was carried out using SPSS Version 25, Japanese version (IBM Corp. Tokyo, Japan).

RESULTS

From February 2015 to December 2018, a total of 36 subjects were enrolled. Till date (February 2019), 6 subjects have been excluded from the study according to the exclusion criteria because of a preoperative modified treatment plan. After the enrollment of 30 participants, who will be followed, the study will end in March 2019.

DISCUSSION

It has been widely accepted that breast or plastic surgeons apply the sling method using ADM or synthetic biomaterial sheets for immediate breast reconstruction with TE/implant or direct-to-implant. However, in present, ADM is not available and used intraoperatively in Japan because of their medical insurance system. Breuing et al described this procedure for immediate breast reconstruction using ADM as a direct implant technique.[20] Since then, there have been many reports about this procedure[2-10]; however, there has also been controversial issues indicating that this procedure causes an increase in postoperative complications.[6] Compared with western countries, there are many women with subdermal soft tissue and skin that is too thin in East Asia, including Japan. These women have poor skin perfusion following mastectomy, so it is predicted that postoperative complications when using the sling method for immediate two stage breast reconstruction will increase in Japan if any inclusion criteria has not been set. Therefore, this study has a protocol with strict inclusion criteria for using NEOVEIL in the sling method referred as an ongoing study.[22] If this study proves safety of this material for sling method in breast reconstruction with TE/implant, it is expected that this procedure can be widely accepted in Japan for patients with certain criteria based on this trial. Some case reports have been described to use a synthetic biomaterial mesh for this technique in Japan, but this material has little evidence. The NEOVEIL sheet was developed as a scaffold in a tissue engineering and regenerative medicine and can be expected to have superior soft tissue regeneration.

The cost of a NEOVEIL sheet is $165 per 10×10 cm, which is not too costly. Thus, this material also has an advantage over the ADM to use with sling method in not only Japan but also in western countries.

There are some limitations to the present study that need to be considered. This is a single-arm interventional study in a single institution. Although further studies are needed, we consider comparing a historical control as an alternative method to evaluate the safety and efficacy of this procedure.

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CONFLICT OF INTEREST

NEOVEIL sheets using in this study will be supported by GUNZE medical division and Kyoto Medical Planning.

REFERENCES

1) Cordeiro PG. Breast reconstruction after surgery for breast cancer. *N Engl J Med*. 2008;359(15):1590–1601.
2) JoAnna NT, Carey JN, Wong AK. Use of human acellular dermal matrix in implant-based breast reconstruction: evaluating the evidence. *J Plast Reconstr Aesthet Surg*. 2011;64(12):1553–1561.
3) Bindingnavele V, Gaon M, Ota KS, Kulber DA, Lee DJ. Use of acellular cadaveric dermis and tissue expansion in postmastectomy breast reconstruction. *J Plast Reconstr Aesthet Surg*. 2007;60(11):1214–1218.
4) Choi M, Frey JD, Alperovich M, Levine JP, Karp NS. "Breast in a Day": examining single-stage immediate, permanent implant reconstruction in nipple-sparing mastectomy. *Plast Reconstr Surg*. 2016;138(2):184e–191e.
5) Rodriguez-Feliz J, Codner MA. Embrace the change: incorporating single-stage implant breast reconstruction into your practice. *Plast Reconstr Surgy*. 2015;136(2):221–231.
6) Kim JY, Davila AA, Persing S, et al. A meta-analysis of human acellular dermis and submuscular tissue expander breast reconstruction. *Plast Reconstr Surg*. 2012;129(1):28–41.
7) Kobraei EM, Nimtz J, Wong L, et al. Risk factors for adverse outcome following skin-sparing mastectomy and immediate prosthetic reconstruction. *Plast Reconstr Surg*. 2012;129(2):234e–41e.
8) Tessler O, Reish RG, Maman DY, Smith BL, Austen WG Jr. Beyond biologics: absorbable mesh as a low-cost, low-complication sling for implant-based breast reconstruction. *Plast Reconstr Surg*. 2014;133(2):90e–99e.
9) Baldelli I, Cardoni G, Franchelli S, et al. Implant-based breast reconstruction using a polyester mesh (Surgimesh-PET): a retrospective single-center study. *Plast Reconstr Surg*. 2016;137(6):931e–939e.
10) Rodriguez-Unda N, Leiva S, Cheng HT, Seal SM, Cooney CM, Rosson GD. Low incidence of complications using polyglactin 910 (Vicryl) mesh in breast reconstruction: a systematic review. *J Plast Reconstr Aesthet Surg*. 2015;68(11):1543–1549.
11) Lin XM, Liu Y, Chi C, Lin CX, Yang Y. Efficacy of an absorbable polyglycolic acid patch in surgery for pneumothorax due to silicosis. *J Cardiothorac Surg*. 2012;7:18.
12) Lee S, Park SY, Bae MK, et al. Efficacy of polyglycolic acid sheet after thoracoscopic bullectomy for spontaneous pneumothorax. *Ann Thorac Surg*. 2013;95(6):1919–1923.
13) Regnault P. Breast ptosis: definition and treatment. *Clin Plast Surg*. 1976;3(2):193–203.
14) Japan clinical oncology group. Japan clinical oncology group postoperative complication criteria (Clavien-Dindo classification) version 2.0 [in Japanese]. http://www.jcog.jp/doctor/tool/Clavien_Dindo.html. Accessed June 25, 2019.
15) Mukai Y, Watanabe S, Matsumoto M, Saiga M, Kimata Y. Reliability and validity of Mamma Balance: novel software to assess the symmetry of the nipple-areola-complex position. *J Plast Reconstr Aesthet Surg*. 2017;70(8):1147–1149.
16) Pusic AL, Klassen AF, Scott AM, Klok JA, Cordeiro PG, Cano SJ. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. *Plast Reconstr Surg*. 2009;124(2):345–353.
17) Tsoi B, Ziolkowski NI, Thoma A, Campbell K, O'Reilly D, Goeree R. Safety of tissue expander/implant versus autologous abdominal tissue breast reconstruction in postmastectomy breast cancer patients: a systematic review and meta-analysis. *Plast Reconstr Surg*. 2014;133(2):234–249.
18) Cordeiro PG, McCarthy CM. A single surgeon's 12-year experience with tissue expander/implant breast reconstruction: part I. A prospective analysis of early complications. *Plast Reconstr Surg*. 2006;118(4):825–831.
19) Cordeiro PG, McCarthy CM. A single surgeon's 12-year experience with tissue expander/implant breast reconstruction: part II. An analysis of long-term complications, aesthetic outcomes, and patient satisfaction. *Plast Reconstr Surg*. 2006;118(4):832–839.
20) Breuing KH, Warren SM. Immediate bilateral breast reconstruction with implants and inferolateral AlloDerm slings. *Annals of plastic surgery*. 2005;55(3):232–239.
21) Susarla SM, Ganske I, Helliwell L, Morris D, Eriksson E, Chun YS. Comparison of clinical outcomes and patient satisfaction in immediate single-stage versus two-stage implant-based breast reconstruction. *Plast Reconstr Surg*. 2015;135(1):1e–8e.
22) Zhong T, Temple-Oberle C, Hofer S, et al. The Multi Centre Canadian Acellular Dermal Matrix Trial (MCCAT): study protocol for a randomized controlled trial in implant-based breast reconstruction. *Trials*. 2013;14:356–367.