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Original Article

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Effect of Poloxamer-Based Thermo-Sensitive Sol-Gel Agent on Upper Limb Dysfunction after Axillary Lymph Node Dissection: A Double-Blind Randomized Clinical Trial

Hee Jun Choi [1,*], **Jai Min Ryu** [2,*], **Byung Joo Chae** [2], **Eun-Kyu Kim** [3], **Jun Won Min** [4], **Hyuk Jai Shin** [5], **Seok Jin Nam** [2], **Jonghan Yu** [2], **Jeong Eon Lee** [2], **Se Kyung Lee** [2], **Seok Won Kim** [2]

[1]Department of Surgery, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea
[2]Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[3]Division of Breast Surgery, Department of Surgery, University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
[4]Department of Surgery, Dankook University College of Medicine, Cheonan, Korea
[5]Department of General Surgery, Myongji Hospital, Goyang, Korea

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Correspondence to
Seok Won Kim
Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
E-mail: seokwon1.kim@samsung.com

*Hee Jun Choi and Jai Min Ryu equally contributed to this work.

ORCID iDs
Hee Jun Choi
https://orcid.org/0000-0002-2601-2187
Jai Min Ryu
https://orcid.org/0000-0001-5405-7385
Byung Joo Chae
https://orcid.org/0000-0003-1564-0978
Eun-Kyu Kim
https://orcid.org/0000-0003-1318-0939
Jun Won Min
https://orcid.org/0000-0001-7440-2561
Hyuk Jai Shin
https://orcid.org/0000-0003-2728-3146
Seok Jin Nam
https://orcid.org/0000-0003-1072-8954

ABSTRACT

Purpose: Restricted shoulder motion is a major morbidity associated with a lower quality of life and disability after axillary lymph node dissection (ALND) in patients with breast cancer. This study sought to evaluate the antiadhesive effect of a poloxamer-based thermosensitive sol-gel (PTAS) agent after ALND.

Methods: We designed a double-blind, multicenter randomized controlled study to evaluate the clinical efficacy and safety of PTAS in reducing upper-limb dysfunction after ALND. The primary outcome was the change in the range of motion (ROM) of the shoulder before surgery and 4 weeks after ALND (early postoperative period). Secondary outcomes were shoulder ROM at six months, axillary web syndrome, and lymphedema (late postoperative period).

Results: A total of 170 patients with planned ALND were randomly assigned to one of 2 groups (poloxamer and control) and 15 patients were excluded. In the poloxamer group (n = 76), PTAS was applied to the surface of the operative field after ALND. ALND was performed without the use of poloxamer in the control group (n = 79). Relative to the control group, the poloxamer group had significantly lower early postoperative restrictions in total shoulder ROM at four weeks (−30.04 ± 27.76 vs. −42.59 ± 36.79; $p = 0.0236$). In particular, the poloxamer group showed greater reductions in horizontal abduction at four weeks (−3.92 ± 9.80 vs. −10.25 ± 15.42; $p = 0.0050$). The ROM of the shoulder at 24 weeks, axillary web syndrome, and lymphedema were not significantly different between the two groups. No adverse effects were observed in either group.

Conclusion: We suggest that poloxamer might improve the early postoperative shoulder ROM in patients with breast cancer who have undergone ALND.

Trial Registration: ClinicalTrials.gov Identifier: NCT02967146

Keywords: Dissection; Poloxamer; Shoulder

Jonghan Yu
https://orcid.org/0000-0001-9546-100X
Jeong Eon Lee
https://orcid.org/0000-0003-0037-2456
Se Kyung Lee
https://orcid.org/0000-0003-1630-1783
Seok Won Kim
https://orcid.org/0000-0002-6130-7570

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Conflict of Interest
The authors declare that they have no competing interests.

Author Contributions
Conceptualization: Choi HJ, Ryu JM, Kim EK, Kim SW; Data curation: Ryu JM, Min JW, Shin HJ, Lee JE, Lee SK, Kim SW; Methodology: Chae BJ, Nam SJ, Kim SW; Supervision: Yu J, Lee JE, Lee SK, Kim SW; Visualization: Nam SJ; Writing - original draft: Choi HJ; Writing - review & editing: Choi HJ, Ryu JM, Kim SW.

INTRODUCTION

Breast cancer is the most frequent cancer found among women, affecting 2.1 million women each year worldwide [1]. According to the statistics of the Korea Central Cancer Registry, breast cancer was the most common cancer in women reported in Korea in 2016 [2]. Early detection and development of surgical treatment and systemic therapy have led to an improvement in the prognosis of breast cancer [3]. Over time, there has been an increase in breast cancer survival, and efforts to improve the quality of life of these patients have been emphasized [4].

Although the era of de-escalation of axillary surgery has been expanding, axillary lymph node dissection (ALND) remains a standard surgical treatment option for breast cancer patients with axillary lymph node metastasis [5,6]. ALND can cause shoulder dysfunction, which influences the quality of life of breast cancer survivors [7,8]. Upper-limb dysfunction is an important complication as it can cause limited motion and severe pain, and various methods exist to reduce such complications [9-11]. However, to our knowledge, there are no studies available on substances that can help with ALND complications.

Poloxamer-based thermosensitive antiadhesive sol-gel (PTAS) agent has received attention because of its potential application as an adhesion-preventing agent in various surgeries. PTAS has the unique ability to change its phase from sol to gel according to the temperature increase; in this manner, PTAS can be easily injected into the target area because it remains in the sol phase at room temperature. Once the PTAS is injected into the body, it immediately forms a gel on the body surface. The gel can act as a mechanical barrier that can prevent tissue adhesion over a few days and can be safely excreted in urine. Poloxamer consists of hydrophilic polyethylene glycol (PEG) and hydrophobic polypropylene glycol (PPG) arranged in a triblock structure (PEGx–PPGy–PEGx) [12]. The hydrophilic PEG blocks of poloxamer, chitosan, and gelatin have mucoadhesive properties. These ingredients ensure that the PTAS gel remains in the applied tissue without dislocation, preventing sticking between tissues [13]. At body temperature, the hydrophobic PPG block dehydrates, and the poloxamer copolymer molecules aggregate into micelles. These micelles are arranged over time and form a gel, acting as a physical barrier to prevent adhesion between adjacent tissues. Previous studies have reported the effect of PTAS on the reduction of postsurgical adhesion formation in animal models [14,15]. Recently, the clinical application of PTAS has also been reported for the prevention of tissue adhesion for various indications, including total knee arthroplasty, endonasal dacryocystorhinostomy, parotidectomy, and prostatectomy [2,16-18].

We hypothesized that the application of PTAS to the axillary surface after ALND would facilitate early recovery of shoulder range of motion (ROM) in patients with breast cancer. The purpose of this study was to evaluate the efficacy and safety of a newly developed PTAS agent in patients undergoing ALND based on a comparison with a control group.

METHODS

Patients

When considering the allocation ratio between groups 1:1 and the significance level of a one-sided test at 2.5% and 80% power, respectively, the number of subjects required for this clinical trial can be obtained through the following formula:

$$n = \frac{(Z_{1-\alpha}+Z_{1-\beta})^2\sigma^2(1+1/k)}{(\mu_T-\mu_C)^2} \approx 72,\ (\sigma = \sqrt{\frac{49\times24.75^2+48\times18.90^2}{50+49-2}} \approx 22.05)$$

As a result, in this clinical trial, 72 test subjects each were required for the test group and the control group, respectively, with a total of 170 test subjects (85 per group) that ultimately participated in the study, considering a dropout rate of approximately 15%. A total of 170 patients who were diagnosed with invasive breast cancer and treated with planned ALND followed by curative surgery at Samsung Medical Center (SMC), Seoul National University Bundang Hospital (SNUBH), Dankook University Hospital (DKUH), and Myongji Hospital (MJH) between December 2016 and December 2018 were selected. As the surgeon who performed ALND directly applies the investigational medicinal product around the surgical area, blinding the operator is impossible; therefore, evaluator-subject blinding was used to maintain the objectivity of the test results. For the evaluation, an independent evaluator, the rehabilitation medicine specialists of each institution, who are not related to this study performed ROM angle evaluation; consequently, group allocation was not disclosed. Therefore, subjects' inclusion in the experimental or control group was known only to the randomization manager who wrote the randomization code, code manager, and surgeon; the independent evaluator was blinded. Patients with bilateral or recurrent breast cancer; a previous history of cancer; selective axillary dissection; immediate reconstruction, or a previous history of arm motion dysfunction including adhesive capsulitis, rotator cuff disease, calcific tendinitis, fracture, or other painful shoulder disease were excluded. Patients with planned ALND were randomly assigned to one of the 2 groups (poloxamer or control) and 15 patients were excluded, including 9 from the poloxamer group and 6 from the control group. Finally, 155 patients were identified as eligible and included in the study (**Figure 1**). All patients received education about rehabilitation and exercise by a rehabilitation doctor who was blinded to the study groups. Most patients received adjuvant chemotherapy, with treatment including anthracycline plus cyclophosphamide, followed by anthracycline-based,

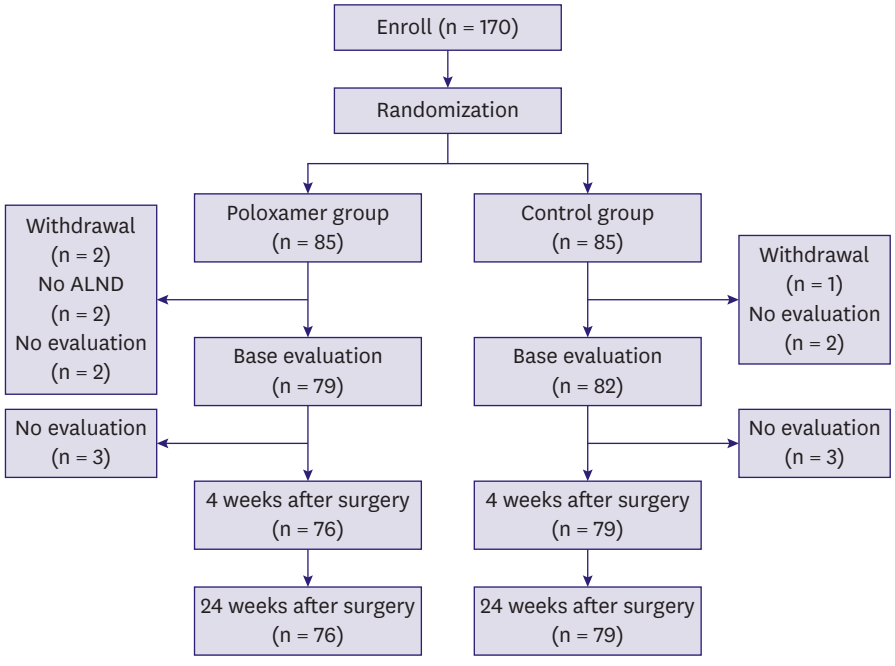

Figure 1. Flowchart of study patients.
ALND = axillary lymph node dissection.

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taxane-based, or trastuzumab regimens. Adjuvant radiotherapy was performed in all patients followed by breast-conserving surgery. Patients who underwent mastectomy were treated with adjuvant radiotherapy if the disease was stage N2 or N3, or stage N1 if they were also considered to be at high risk according to perinodal extension, lymphovascular invasion, or high nuclear grade by the doctor. Most ALND procedures involve lymph node dissection at levels I and II. Level III dissection was completed when there was a suspicious node at level II. Radiotherapy to the supraclavicular fossa was performed in patients with disease of greater than stage N2.

Interventions

This study was a prospective, double-blind, multicenter randomized controlled study to evaluate the clinical efficacy and safety of PTAS in reducing upper-limb dysfunction after ALND. Patients were randomly assigned to either the poloxamer or the control group using a randomized technique by a clinical researcher who was blinded to the study. Randomization of the two groups at a ratio of 1:1 was achieved using a stratified randomization procedure. In each hospital, only one dedicated rehabilitation doctor performed the protocol to reduce interobserver variability.

Commercially available PTAS (Mediclore; CGbio Co., Ltd. Seongnam, Korea) was used in this study. This agent was manufactured by boiling sterile water at 60°C and dissolving chitosan, gelatin, and poloxamer 188/407. The agent was stored at 0°C–4°C, filled, and packed in a sterile syringe and sealed in a PET tray and Tyvek film (DuPont, Wilmington, USA). Finally, the product was sterilized using an electron beam. This PTAS agent allows solution-to-gel transition with a lower critical solution temperature of 28°C–30°C. In the poloxamer group, PTAS was applied evenly to the surface of all axillary operation after ALND. However, no intervention was performed in patients in the control group. All ALND cases underwent lymph node dissection at levels I/II, with some also undergoing dissection at level III.

Outcome measurement

All outcome data were collected prospectively at baseline, and 4 and 24 weeks postoperatively by a rehabilitation doctor who was blinded to the study group allocation. The primary outcome was shoulder ROM. ROM was defined as the sum of forward flexion and horizontal abduction before and after ALND. Horizontal abduction was measured with the patient moving their straight arm with thumb up and elbow extended posteriorly after abducting the arm 90° (**Figure 2**). ROM referred to the sum of forward flexion and horizontal abduction before surgery (baseline) and 4 weeks after ALND. Secondary outcomes included ROM of the shoulder at 24 weeks, internal rotation, external rotation, abduction, disabilities of the arm, shoulder, and hand (DASH), numerical rating scale (NRS), axillary web syndrome, and lymphedema at 4 weeks and 24 weeks after surgery. We checked for the presence of a palpable or visible cord to identify axillary web syndrome and assessed the feeling of tightness or restriction in shoulder ROM. If edema of patient was suspected in the Department of Rehabilitation at 4 and 24 weeks postoperatively, the arm circumference 10 cm above and below the elbow was measured.

Safety assessment

Adverse events that occurred after the application of PTAS based on causal relationships were investigated throughout the study period. We mainly studied skin and subcutaneous tissue disorders, wound infection, fever incidence, and allergy symptoms in the 2 groups (**Supplementary Table 1**).

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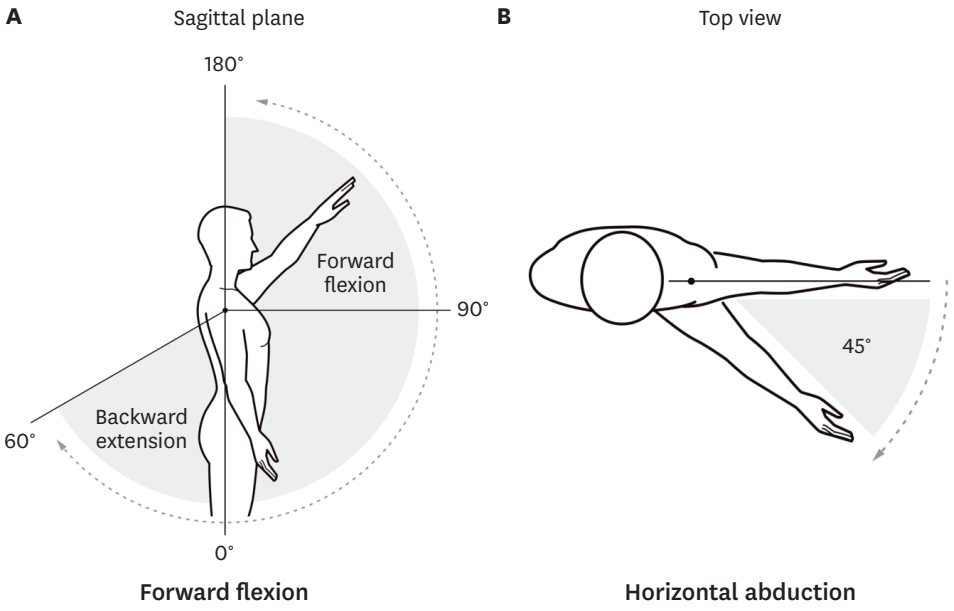

Figure 2. Method to measure the range of motion of the shoulder. (A) Forward flexion; (B) Horizontal abduction.

Statistics

R (version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria) and the T&F version 2.9 (YooJin BioSoft, Goyang, Korea) were used for all statistical analyses. Data are expressed as mean ± standard deviation for continuous variables. When the variables were normally distributed, the mean difference test between the two sample groups was compared using Student's t-test or Welch's t-test. For non-normally distributed variables, the Mann-Whitney U test (for the sample groups) was used. For categorical variables, the chi-squared test or Fisher's exact test was used to compare the proportions of sample numbers as appropriate. Differences were considered significant when the *p*-value was less than 0.05.

Ethical approval

This study adhered to the ethical tenets of the Declaration of Helsinki and was approved by the Institutional Review Boards (IRBs) of SMC, SNUBH, DKUH, and MJH, Korea (IRB file No. 2016-08-194, SNUBH-1610/366-001, DKUH 2016-09-002-001, and MJH-16-114) [19]. The study was also registered as a randomized controlled trial at ClinicalTrials.gov (NCT02967146).

RESULTS

In this study, 170 patients with planned ALND were randomly assigned to one of the two groups and 15 patients were excluded. In the poloxamer group (n = 76), PTAS was applied to the surface of the operation field after ALND, while, in the control group (n = 79), ALND was performed without the use of poloxamer (**Figure 1**). The median age of the patients at the time of surgery was 49.39 years. Age, body mass index, number of removed lymph nodes, T-stage, and N-stage, which may affect shoulder movement after surgery, exhibited no significant differences between the two groups. The demographic and clinicopathological characteristics of the patients included in this study are showed in **Table 1**. Some patients with aspiration node-positive invasive breast cancer who underwent NAC had T0/Tis or N0 in pathology.

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Table 1. Clinicopathological and treatment characteristics of patients

Characteristic	Poloxamer group (n = 76)	Control group (n = 79)	Total (n = 155)	*p*-value
Age (yr)	49.57 ± 9.56	49.23 ± 9.68	49.39 ± 9.59	0.8272
Range	23–74	25–78	23–78	
BMI (kg/m^2)	23.86 ± 3.59	23.93 ± 3.53	23.90 ± 3.55	0.9636
Breast cancer subtype				0.5826
HR+HER2−	37 (48.68)	41 (51.90)	78 (50.32)	
HR+HER2+	11 (14.47)	12 (15.19)	23 (14.84)	
HR−HER2+	15 (19.74)	16 (20.26)	31 (20.00)	
TNBC	13 (17.11)	10 (12.66)	23 (14.84)	
Neoadjuvant chemotherapy	41 (53.95)	33 (41.77)	74 (47.74)	0.1769
Tumor stage				0.8154
T0-Tis	12 (15.79)	15 (18.99)	27 (17.42)	
T1	46 (60.53)	45 (56.96)	91 (58.71)	
T2	17 (22.37)	17 (21.52)	34 (21.94)	
T3	1 (1.31)	2 (2.53)	3 (1.93)	
Nodal stage				0.3379
N0	33 (46.05)	27 (34.18)	60 (38.71)	
N1	19 (21.05)	27 (34.18)	46 (29.68)	
N2	22 (25.32)	23 (29.11)	45 (29.03)	
N3	2 (2.53)	2 (2.53)	4 (2.58)	
Types of surgery				0.3976
Mastectomy with ALND	37 (48.68)	42 (53.16)	79 (50.97)	
Breast conserving surgery with ALND	39 (51.32)	37 (46.84)	76 (49.03)	
Number of resected lymph nodes	18.01 ± 9.27	18.09 ± 7.50	18.05 ± 8.39	0.7000
Radiotherapy				0.8379
Yes	62 (81.58)	65 (82.28)	127 (81.94))	
No	14 (18.42)	14 (17.72)	28 (18.06)	

Values are presented as mean ± standard deviation or number (%) not otherwise specified.
BMI = body mass index; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer; ALND = axillary lymph node dissection.

At the baseline evaluation, the total shoulder ROM was comparable between the 2 groups (221.85 ± 12.85 in the poloxamer group vs. 223.72 ± 12.54 in the control group; $p = 0.1183$). At four weeks after surgery, the mean change in the total shoulder ROM from baseline evaluation was −30.04° ± 27.76° in the poloxamer group and −42.59° ± 36.79° in the control group. There was a significant difference between the two groups at 4 weeks ($p = 0.0236$). At 24 weeks after surgery, the mean change in the total shoulder ROM from baseline evaluation was −13.53° ± 24.98° in the poloxamer group and −8.89° ± 22.22° in the control group ($p = 0.8837$). Significant meaningful differences in the change in ROM were apparent at 4 weeks in the 2 intervention groups. Greater reductions in horizontal abduction at four weeks (−3.92 ± 9.80 vs. −10.25 ± 15.42, change from baseline; $p = 0.0050$) were observed especially in the poloxamer group.

There were no significant differences in forward flexion, internal rotation, external rotation, or abduction between the two groups at 4 and 24 weeks. DASH, axillary web syndrome, and lymphedema were not significantly different between the 2 groups. The clinical movements of the patients included in this study are shown in **Table 2**. No adverse effects were observed in either group during the 24 weeks of treatment (**Supplementary Table 1**).

DISCUSSION

This double-blind, multicenter randomized controlled study found that PTAS improved shoulder ROM by reducing early axillary postoperative adhesions. The effect of poloxamer was apparent as a significant antiadhesive effect at four weeks after ALND and no adverse

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Table 2. Clinical shoulder movement and outcome after 4 weeks and 24 weeks of surgery

Variables	Poloxamer group	Control group	*p*-value
Sum of ROM			
Baseline	221.85 ± 12.68	223.72 ± 12.54	0.1183
4 weeks after surgery	182.15 ± 36.51	192.21 ± 30.01	
4 weeks change from baseline	−30.04 ± 27.76	−42.59 ± 36.79	0.0236
24 weeks after surgery	205.48 ± 32.10	207.59 ± 27.63	
24 weeks change from baseline	−13.53 ± 24.98	−8.89 ± 22.22	0.8837
Forward flexion			
4 weeks change from baseline	−26.58 ± 25.65	−32.90 ± 30.01	0.1643
24 weeks change from baseline	−12.04 ± 22.82	−9.09 ± 20.29	0.3760
Horizontal abduction			
4 weeks change from baseline	−3.92 ± 9.80	−10.25 ± 15.42	0.0050
24 weeks change from baseline	−4.33 ± 10.64	−7.05 ± 13.72	0.1955
Internal rotation			
4 weeks change from baseline	−1.49 ± 8.63	0.30 ± 8.01	0.2081
24 weeks change from baseline	−4.41 ± 14.07	−3.37 ± 16.41	0.7306
External rotation			
4 weeks change from baseline	−0.32 ± 2.02	0.37 ± 6.74	0.4213
24 weeks change from baseline	−3.99 ± 12.82	−0.73 ± 10.00	0.0826
Abduction			
4 weeks change from baseline	−34.35 ± 34.97	−39.44 ± 38.63	0.4002
24 weeks change from baseline	−15.43 ± 31.68	−10.55 ± 28.07	0.3115
DASH			
4 weeks change from baseline	26.37 ± 16.58	31.04 ± 19.10	0.1472
24 weeks change from baseline	19.68 ± 18.67	16.61 ± 17.32	0.1093
NRS			
4 weeks change from baseline	1.90 ± 2.75	2.36 ± 2.54	0.2958
24 weeks change from baseline	1.10 ± 2.33	1.06 ± 1.92	0.8870
Axillary web syndrome			
4 weeks	7 (8.97)	10 (12.35)	0.4916
24 weeks	7 (8.97)	8 (9.76)	0.8653
Lymphedema			
4 weeks	2 (2.56)	6 (7.41)	0.2771
24 weeks	6 (7.69)	14 (17.07)	0.0729

Values are presented as mean ± standard deviation not otherwise specified.
ROM = range of motion; DASH = disabilities of the arm, shoulder, and hand; NRS = numerical rating scale.

effects were noted during the 6 months following the application of poloxamer. In addition, this study is the first trial to evaluate the effects of poloxamer on shoulder movement after ALND in patients with breast cancer.

The poloxamer used in this investigation was composed of chitosan and gelatin. The positively charged chitosan also facilitates adhesion to the mucous membrane. Chitosan is also known to be biocompatible, biodegradable, nontoxic, and nonallergenic in nature [20-23]. Poloxamer biodegrades easily in the body and is excreted through the urinary system, which is an important feature when considering safety or the prevention of foreign-body reactions [24]. None of the patients in our study showed any side effects associated with the use of this material. Poloxamer has been used in hemostats, wound dressings, tissue adhesives, and as drug- and cell-delivery carriers [25-27]. The efficacy of PTAS has been widely reported in many kinds of surgeries with the aim of reducing adhesion [16-18,27]. Chung et al. [17] conducted a randomized controlled trial to assess the effect of PTAS in patients with benign prostatic hyperplasia who underwent transurethral resection of the prostate. In their study, patients instilled with PTAS showed a better maximum urinary flow rate (Q_{max}) than the control group (poloxamer group vs. control group: 18.92 [9.98]] vs. 15.58 [9.24] mL/s; $p = 0.028$), while urethral stricture after transurethral resection of the prostate was found in 2 of 80 patients

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in the poloxamer group and 10 of 83 patients in the control group ($p = 0.023$). Nam et al. [16] demonstrated the effects of PTAS on functional recovery of the greater auricular nerve after parotidectomy. They reported tactile sensation and warm sensation in the ear lobule and a warm sensation in the mastoid area, suggesting significant improvement at 24 weeks postoperatively in the poloxamer group, thereby revealing a reduction in the level of discomfort in patients following the application of PTAS after parotidectomy.

The relevance of a variable effect on ROM between the 2 groups is debatable. However, compared with the control group, the poloxamer group showed a significant reduction in early postoperative restriction of total shoulder ROM at 4 weeks, which suggests the PTAS facilitates early recovery from ROM dysfunction. Bendz and Fagevik Olsén [28] reported that shoulder mobility in the early shoulder exercise group was recovered significantly earlier on than that in the delayed shoulder exercise group after ALND. In other words, shoulder exercise during the early postoperative period could reduce shoulder dysfunction. The PTAS agent in the ALND group also reduced adhesion formation and promoted early recovery from ROM dysfunction. These effects help patients to achieve early rehabilitation. Early ROM recovery can help patients return to their activities of daily living [28,29].

To the best of our knowledge, no previous studies have established which treatments can help with ALND-related complications. Previously, only a single study suggested the application of hyaluronate and carboxymethyl cellulose on the pectoralis muscles after mastectomy followed by improvements in shoulder ROM [30]. In this study, we evaluated shoulder ROM and morbidity after ALND in the both groups. The poloxamer group showed a greater reduction in horizontal abduction ($p = 0.0050$) than in internal rotation ($p = 0.2081$) at 4 weeks. Interestingly, meaningful results were observed with respect to shoulder ROM ($p = 0.236$) at 4 weeks but not at 24 weeks ($p = 0.8837$), which could be related to the body's natural ability to recover over time. Lymphedema tended to improve slightly at 24 weeks, but the results were not significant. Therefore, a longer study duration is essential.

Although the number of patients in our study was relatively small, our study was a double-blind randomized controlled study. Although neoadjuvant chemotherapy and non neoadjuvant chemotherapy patients may have been mixed, the characteristics of both groups were evenly distributed. The present results, although from small number of participating patients, are considered meaningful and allow us to confidently draw significant conclusions. In addition, as the present study was performed at multiple centers and institutions located in Korea, any bias caused by the involvement of a single surgeon was avoided. However, the cost was greater than that for the control group and there was no direct positive effect on the timing of long-term recovery.

In conclusion, our results provide evidence that poloxamer might improve horizontal abduction of the shoulder in breast cancer patients with ALND.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Incidence of adverse effect after double blind clinical trial by causal relationship

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