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Effect of Antiadhesion Barrier Solution and Fibrin on Capsular Formation After Silicone Implant Insertion in a White Rat Model

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Abstract

Introduction One of the most serious complications of breast reconstruction and augmentation using silicone implants is capsular contracture. Several preventive treatments, including vitamin E, steroids, antibiotics, and cysteinyl leukotriene inhibitors, have been studied, and their clinical effects have been reported. However, the problem of capsular contracture has not yet been completely resolved. This study was performed to compare antiadhesion barrier solution (AABS) and fibrin in their ability to prevent fibrotic capsule formation and simultaneously evaluated their effect when used in combination by capsular thickness analysis and quantitative analysis of matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), and type I collagen within the fibrous capsule.

Materials and Methods This study used female six-week-old Sprague-Dawley rats. Eighty rats were equally subdivided into the four following groups: AABS-treated, fibrin-treated, AABS and fibrin combined-treated, and untreated control groups. Each rat received two silicone chips under the panniculus carnosus muscle layer. The test materials were applied around the silicon chips. Four weeks later, the implantation sites including the skin and muscle were excised to avoid the risk of losing the fibrous capsule around the implants. The capsular thickness was analyzed by Masson's trichrome stain. Quantitative analysis of type I collagen, MMPs, and TIMPs was performed by real-time PCR, Western blot, and zymography.

Results The mean capsular thickness was 668.10 ± 275.12 μm in the control group, 356.97 ± 112.11 μm in the AABS-treated group, 525.96 ± 130.97 μm in the fibrin-treated group, and 389.24 ± 130.51 μm in the AABS and fibrin combined-treated group. Capsular thickness was significantly decreased in all experimental groups ($p < 0.05$). Capsular thickness was greater in the fibrin-treated group than in the AABS-treated group ($p < 0.05$). There was no statistically significant difference in capsular thickness between the AABS and fibrin combined-treated group and the AABS- or fibrin-treated group ($p > 0.05$). Compared to the control group, the experimental groups had significantly lower expressions of type I collagen and MMP-1 ($p < 0.05$), but there was no statistically significant difference in expressions of type I collagen and MMP-1 between the AABS-, fibrin-, and AABS and fibrin combined-treated groups ($p > 0.05$). The expressions of MMP-2 and TIMP-2 were not significantly different between the control and the experimental groups ($p > 0.05$).

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Conclusion AABS is more effective in reducing capsular thickness compared with fibrin treatment in a white rat model.

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Keywords Fibrin · Implant capsular contracture · Silicone · Collagen · MMPs · TIMP

Introduction

Capsular contracture is one of the most serious complications that can develop after breast reconstruction and augmentation using silicone implants [1]. Capsular contracture often leads to pain, hardening of breast texture, some esthetic failure, and often requires restorative surgery such as capsulotomy, capsulectomy, or even implant removal. In breast reconstruction surgery after mastectomy, it is especially difficult to perform restorative surgery to treat capsular contracture owing to the lack of original tissue and skin. In such cases, primary prevention of capsular contracture is extremely important.

The pathologic process of capsular contracture is triggered by individual reactivity to silicone, the anatomical position of the implant, bacterial contamination, and certain perioperative complications such as hematomas or seromas [2–4]. Based on these factors, several pharmacological preventive treatments using vitamin E, steroids, antibiotics, and cysteinyl leukotriene inhibitors have been studied, and their clinical effects have been reported [5–8]. However, the problem of capsular contracture has not yet been completely resolved. Recently, anti-adhesion barrier solution (AABS) has been shown to be effective in preventing capsular contracture [9]. AABS is a transparent and slightly viscous substance, consisting of sodium hyaluronate and sodium carboxymethylcellulose. Karaçal et al. [10] reported that hyaluronate-containing amniotic fluid was effective in reducing capsule thickness, and carboxymethylcellulose is well known for its postoperative adhesion-reducing effect [11, 12]. A well-known film-type product, Seprafilm (Genzyme Biosurgery, USA), has the same components and is widely recognized for its effectiveness in preventing adhesion after abdominal and pelvic surgery [13, 14]. Autologous fibrin glue is known as contracture-inducing agent [15]; however, Marques et al. [16] have suggested that commercially available products containing fibrin play a role in preventing capsular contracture. Fibrin-containing commercial products are widely used in clinical settings and may be useful during surgeries such as dual-plane augmentation mammoplasties, which are accompanied by muscle dissection. Both AABS and fibrin glue have low systemic side effects and are easy to apply. However, care must be taken to prevent their indiscriminate use because a large amount is needed during breast reconstruction and augmentation. These two compounds also function using different mechanisms to prevent fibrosis. To our knowledge, this is the first study evaluating the combined treatment regimen of AABS and fibrin, to prevent fibrosis.

Breast implants cause an immunological response to the foreign material and the formation of a fibrous capsule surrounding the implants [17–20]. This immunologic response arises within a few days, after the capsule forms, the reaction diminishes and ceases in most cases [20, 21]. However, occasionally, the immune response continues, leading to the formation of a thicker fibrous capsule, composed mainly of type I collagen [17, 22]. Thus, persistent and excessive fibrosis around the implant may be the key contributor to capsular contracture [23]. This progressive fibrosis is a complex process that includes a cascade of molecular events involving several enzymes. The major enzymes involved in the degradation of the extracellular matrix are matrix metalloproteinases (MMPs) [24], which in turn are regulated by tissue inhibitors of metalloproteinases (TIMPs) [25]. The pathogenesis of excessive fibrosis around silicone implants is similar to that of other fibrotic diseases affecting organs such as the liver, skin, lungs, and heart [22]. In these diseases, MMPs and TIMPs play an important role during progressive fibrosis [26]. Among them, MMP-1 (interstitial collagenase), MMP-2 (gelatinase, collagenase), and MMP-9 (gelatinase, collagenase) are involved in tissue maintenance and wound repair [27]. Alterations in the expression of TIMPs play an important role in various fibroproliferative diseases [28]. Ulrich et al. demonstrated the expressions of MMP-1, MMP-2, MMP-9, TIMP-1, and TIMP-2 [22, 29]. In their study, the concentrations of MMP-2, TIMP-1, and TIMP-2 were significantly higher in the serum of patients with capsular contracture [29]. Additionally, the expressions of MMP-2, TIMP-1, and TIMP-2 were significantly higher in tissues of patients with textured implants and capsular contracture grades II and III/IV than in those with grade I [22].

In this study, we compared AABS and fibrin in their ability to prevent fibrotic capsule formation and simultaneously evaluated their effect when used in combination by capsular thickness analysis and the quantitative analysis of type I collagen within fibrous capsules. The design of this

study had some similarity to the study of Ulrich et al. in humans [22, 29], so we evaluated the effects of AABS, fibrin, and the combined use of the two in MMP- 1, 2, and TIMP-2.

Materials and Methods

Experimental Design

This study was approved by Korea University Institutional Animal Care and Use Committee. All applicable institutional guidelines for the care and use of animals were followed. Eighty rats were equally divided into four groups: control, AABS (Guardix-sol®, Genewell, a Dongsung company, Seongnam, Gyeonggi-do, South Korea), fibrin (Tisseel®, Baxter AG, Industriestraße 67, A-1220, Wien, Austria), combined AABS, and fibrin-treated groups. Each rat received two silicone chips, and test materials were applied around these silicon chips. Four weeks later, the implantation sites including the skin and muscle were excised to avoid the risk of losing the fibrous capsule around the implants. One specimen was prepared for histopathological analysis of capsular thickness, and another was used for the quantitative analysis of type I collagen, MMP-1, 2, and TIMP-2.

Implants

A rectangular silicone block, $10 \times 10 \times 2$ mm^3 in size, was generated by cutting envelopes of a commercial breast expander, smooth type (Natrelle®, Allergan, Marlow International, Parkway, Marlow, Bucks, SL7 1YL, United Kingdom). Ethylene oxide sterilization was performed according to the manufacturer's instruction prior to use to prevent contamination or infection.

Experimental Animals

Six-week-old female Sprague-Dawley rats were used for this study. The rats were subjected to a one-week adaptation period prior to the start of the study. To control the risk of infection, feeding and surgical procedures were performed within a specific pathogen-free area of the laboratory animal research center (Korea University, College of Medicine), which operates in accordance with the 8th Guide for the Care and Use of Laboratory Animals. The feeding environment conditions included a twelve-hour photoperiod, humidity of 50 ± 10 %, a temperature of 23 ± 2 °C, and ad libitum feed (vacuum packed, irradiation with 10 kGy). Two animals were housed in each cage.

Surgical Procedures

Each rat was anesthetized using intraperitoneal Zoletil (hydrochlorate tiletamine and hydrochlorate zolepam) 30 mg/kg and xylazine (Rompun) 10 mg/kg. A prophylactic antibiotic (Enrofloxacin at 5 mg/kg, intramuscular) was used to prevent any potential infection resulting from surgery. Dorsal hair was clipped with electrical shears, the skin was painted with 10 % povidone-iodine solution, and the rats were individually draped. Under strict aseptic conditions, a 1-cm midline longitudinal incision was made over the spine at the scapular level, following which the incision was deepened to under the panniculus carnosus muscle. By blunt dissection, an avascular pocket was exposed laterally on both sides of the incision, (Fig. 1) and the implants were inserted into the pocket. We inserted two implants into an experimental animal on both sides of the incision. Following this, 0.1 mL saline of was applied around the implants of control group rats, and 0.1 mL AABS or fibrin was sprayed around the implants of treatment groups. For the combined AABS and fibrin-treated group, 0.05 mL of fibrin was first applied followed by an equal volume of AABS. The wound was closed with nylon 5/0, interrupted vertical mattress sutures. Wound checkup was performed daily. Wound dehiscence was observed in five animals (two in the control group and one in each of the three experimental groups). Lack of infection was confirmed; thus, there was no need to remove the implants, and the wound was simply surgically repaired under anesthesia. After four weeks, the rats were sacrificed under anesthesia (Zoletil 30 mg/kg under CO_2) and surgical specimens from all rats were prepared postmortem. The samples for thickness evaluation were obtained by en bloc resection around the implant including the skin. The

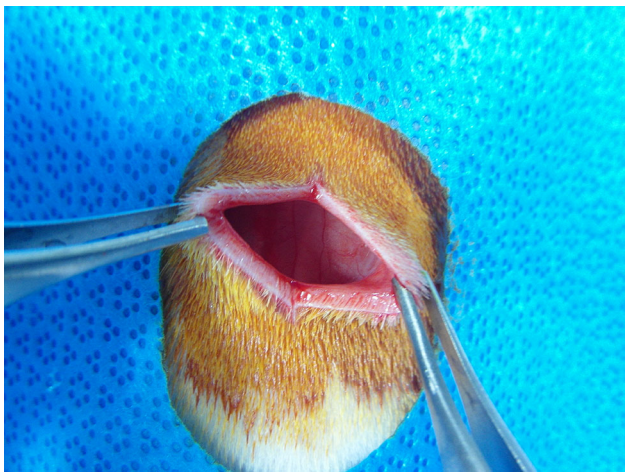

Fig. 1 Image showing the intraoperative procedure. An avascular pocket was exposed laterally on both sides of the incision, and implants were inserted into the pocket

samples for RNA study were taken from the capsule of another implant. The samples for thickness evaluation were fixed in 10 % formalin, and those for quantitative evaluation were frozen in liquid nitrogen immediately after surgical removal.

Capsule Thickness Evaluation

The specimens were fixed in 10 % formalin and 24 h later, they were sectioned into three different full-thickness vertical incisions (right, center, and left), and embedded in paraffin. They were then stained with trichromic Masson's coloration. Under light microscopic examination (Olympus BX40 microscope, DP72 camera and DP controller, Olympus, Tokyo, Japan), capsular thickness was measured for three different areas in three different sections (Figure 2). A total of nine measurements were obtained for each sample, and a mean measurement was calculated.

Real-Time PCR

Total RNA was extracted from biopsied rat samples using the TRIzol reagent (Invitrogen, Carlsbad, CA), according to the manufacturer's instruction. Isolated RNA samples were then used for RT-PCR. Samples (1 μg of total RNA) were reverse transcribed into cDNA in 20 μL of reaction volumes using a first-strand cDNA synthesis kit for RT-PCR, according to the manufacturer's instructions (MBI Fermentas, Hanover, MD).

Gene expression was quantified by real-time PCR using a SensiMix SYBR Kit (Bioline Ltd., London) and 100 ng of cDNA per reaction. The sequences of the primer sets used for this analysis were as follows: rat type I collagen (forward, 5′-GCC AAG ACG AAG ACA TCC CA-3′; reverse, 5′- CCA CAC GTC TCG GTC ATG G-3′), MMP-1 (forward, 5′-TGG GGT CTC ACC ATG CC-3′; reverse, 5′-ATT TCA GGA GGC CGA GGC AG-3′), TIMP-2 (forward, 5′-ACA GAG GGT AAT GTG CAT CTT G-3′; reverse, 5′-TGG ACG TTG GAG GAA AGA AG-3′), and GAPDH as an internal control (forward, 5′-ATT GTT GCC ATC AAT GAC CC-3′; reverse, 5′-AGT AGA GGC AGG GAT GAT GT-3′). An annealing temperature of 60 °C was used for all the primers. PCRs were performed in a standard 384-well plate format with an ABI 7900HT real-time PCR detection system. For data analysis, the raw threshold cycle (C_T) value was first normalized to that of GAPDH for

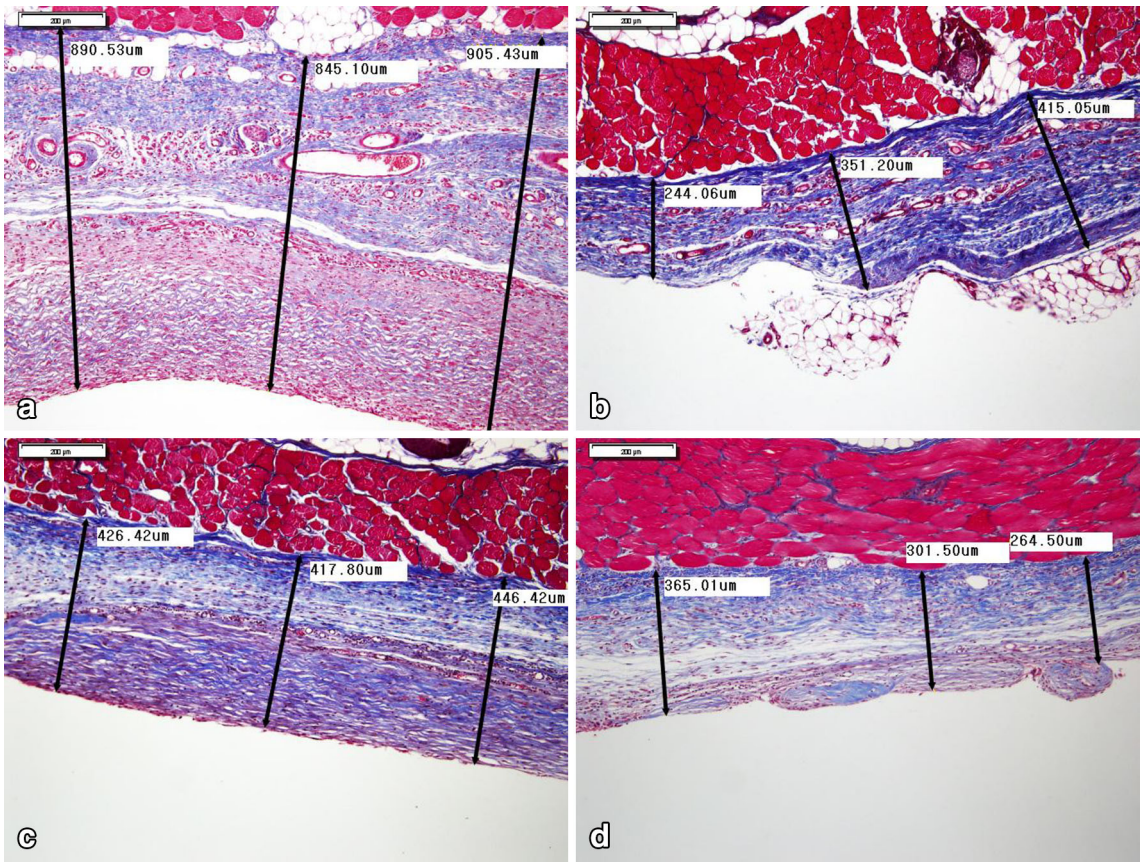

Fig. 2 Histologic view of the capsular thickness (Masson trichrome stain, ×100). The capsular thickness was noticeably decreased in all experimental groups (**a** control group, **b** AABS-treated group, **c** Fibrin-treated group **d** combined AABS and fibrin-treated groups)

each sample to get the ΔC_T. The normalized ΔC_T was then calibrated to the control samples to get the $\Delta\Delta C_T$.

Western Blotting

Rat tissues were homogenized in ice-cold lysis buffer [50 mM Tris–HCl, pH 7.4, 150 mM NaCl, 2 mM EDTA, 5 mM PMSF, 1 mM DTT, and 1 % Triton X-100] with a freshly prepared protease/phosphatase inhibitor cocktail (GenDEPOT, Baker, TX). Homogenates were centrifuged at 13,000 rpm for 15 min at 4 °C, and supernatants were then collected and stored at −70 °C. The concentration of protein in the supernatants was determined using the Bio-Rad Protein Assay Kit (Hercules, CA, USA). Equivalent quantities of protein from each sample were boiled for 5 min in Laemmli sample buffer and then resolved over 8 % SDS-PAGE gels. The separated proteins were electrophoretically transferred onto PVDF membranes. The membranes were subsequently blocked with 10 % skim milk in TBS with 0.01 % Tween-20 for 15 min. at room temperature and incubated with antibodies to type I collagen, MMP-1 (Neomarkers, Fremont, CA), and β-actin (Santa Cruz Biotechnology, Santa Cruz, CA) in 1 % TBS/T buffer (0.01 % Tween-20 in TBS) at 4 °C overnight. The blots were washed 3 times in TBS with 0.01 % Tween-20 and were subsequently incubated with anti-rabbit and anti-mouse HRP-conjugated antibodies (1/2,000 dilution) in TBS/T buffer. After 1 h incubation at room temperature, the blots were washed three times and ECL prime reagents were used for development. Signal densities were quantified using a densitometric program (Bio 1D; Vilber Lourmat, Marne La Vallec, France).

Zymography

Extracted proteins were resuspended in loading buffer [250 mM Tris–HCl, pH 6.8, 10 % SDS, 25 % glycerol, 0.1 % bromophenol blue], and resolved on a 10 % SDS-PAGE gel containing 0.5 mg/mL gelatin without prior denaturation. After electrophoresis, the gels were washed to remove SDS and incubated for 30 min at room temperature in a renaturing buffer (50 mM Tris, 5 mM $CaCl_2$, 0.02 % NaN_3, and 1 % Triton X-100). Next, the gels were incubated for 48 h at 37 °C in a developing buffer [50 mM Tris-HCl (pH 7.8), 5 mM CaCl2, 0.15 M NaCl, and 1 % Triton X-100]. The gels were subsequently stained with Coomassie brilliant blue G-250, destained in 30 % methanol, and flooded with 10 % acetic acid to detect gelatinase secretion. Signal densities were quantified using a densitometric program (Bio 1D; Vilber Lourmat, Marne La Vallec, France).

Statistical Analysis

The data obtained from the capsular thickness analysis were analyzed by one-way ANOVA and those obtained from the quantitative analysis of collagen type I, MMPs, and TIMPs were analyzed by *t* test with the level of significance set at $p < 0.05$.

Results

Capsular Thickness

The mean capsular thickness was 668.10 ± 275.12 μm in the control group, 356.97 ± 112.11 μm in the AABS-treated group, 525.96 ± 130.97 μm in the fibrin-treated group, and 389.24 ± 130.51 μm in the AABS and fibrin combined-treated group. The capsular thickness was significantly decreased in all experimental groups ($p < 0.05$; Fig. 3). The capsular thickness was greater in the fibrin-treated group than the AABS-treated group ($p < 0.05$). There was no statistically significant difference between the AABS and fibrin combined-treated group and AABS- or fibrin-treated groups ($p > 0.05$).

Type 1 Collagen, MMP-1, and TIMP-2 mRNA Levels

Compared to the control group, the experimental groups had significantly lower type I collagen and MMP-1 mRNA levels ($p < 0.05$); however, there was no statistically significant difference in the type I collagen and MMP-1

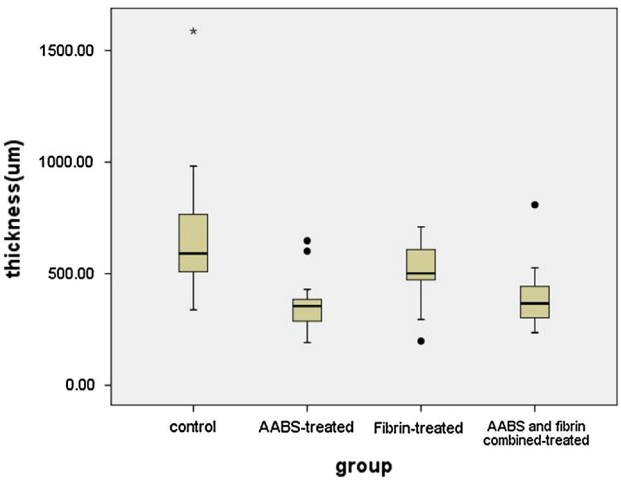

Fig. 3 Average capsular thickness. The capsular thickness was significantly decreased in all experimental groups ($p < 0.05$). The capsular thickness was greater in the fibrin-treated group than in the AABS-treated group ($p < 0.05$). No significant differences were observed between the combined AABS- and fibrin-treated group and AABS- or fibrin-treated groups ($p > 0.05$)

mRNA levels between the AABS-treated, fibrin-treated, and the AABS and fibrin combined-treated groups ($p > 0.05$; Fig. 4).

TIMP-2 mRNA levels were not significantly different between the control and the experimental groups ($p > 0.05$; Fig. 4).

Western Blotting and Zymography

In Western blotting, the protein density of type I collagen and MMP-1 was lower in the experimental groups than in the control group ($p < 0.05$; Figs. 5, 6). Among the experimental groups, there was no statistically significant difference in the protein density of type I collagen and MMP-1 ($p > 0.05$). Using zymography, the protein density of MMP-2 was not significantly different between the control and the experimental groups ($p > 0.05$).

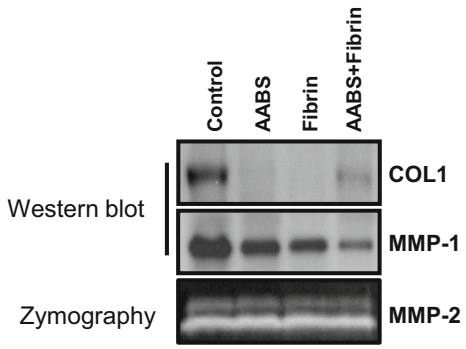

Fig. 5 The Western blot and zymography

Discussion

The pathogenesis of excessive fibrous capsule formation around silicone implants is unclear. Because several factors affect capsule formation, effective prevention of capsular contracture is very difficult. Several chemicals and surgical methods have been used to reduce peri-implant fibrosis. Recently, AABS and fibrin have been reported to be effective in preventing capsular contracture in animal models [9, 16, 30]. In this study, we evaluated the ability of AABS, fibrin, and a combined use of the two in preventing capsular formation.

Lew et al. [9] observed that AABS reduced capsular thickness and showed a tendency to reduce, albeit without any statistical significance, the number of myofibroblasts, which are known to play an important role in the occurrence of capsular contracture. In another study investigating the effect of AABS on capsular contracture, AABS was found to reduce capsular thickness, but had no effect on the intracapsular pressure and the average number of myofibroblasts [30]. Marques et al. observed that fibrin did not affect capsular thickness but resulted in a significantly decreased intracapsular pressure, which could eventually reduce capsular contracture [16]. In this study, we observed that AABS had effects on capsular thickness that were similar to those reported in other studies [9, 30]. However, in contrast to the study by Marques et al., we observed that fibrin reduced capsular thickness. In addition, the combined use of both AABS and fibrin also reduced capsular thickness. In the comparison among the experimental groups, AABS was more effective in reducing capsular thickness than fibrin. Because AABS and fibrin function through different mechanisms, we expected to find synergistic or antagonistic effects when they were used in combination; however, in contrast, it was found that there was no difference between the individual and combined treatments of AABS and fibrin.

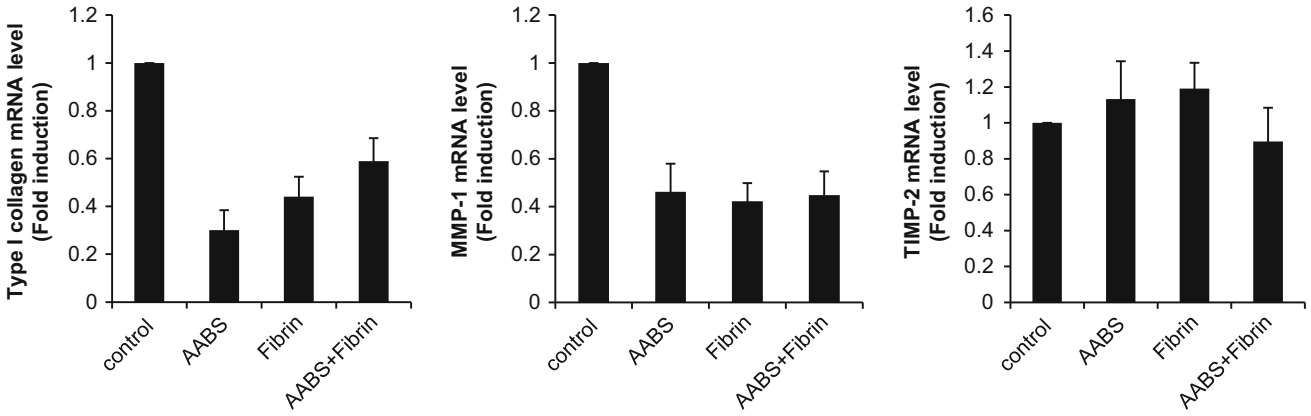

Fig. 4 Relative mRNA expression. Compared to the control group, the experimental groups had significantly lower type I collagen and MMP-1 mRNA levels ($p < 0.05$). However, no significant differences in the type I collagen and MMP-1 mRNA levels were observed between the AABS-treated, fibrin-treated, the combined AABS, and fibrin-treated groups ($p > 0.05$). TIMP-2 mRNA levels were not significantly different between the control and experimental groups ($p > 0.05$)

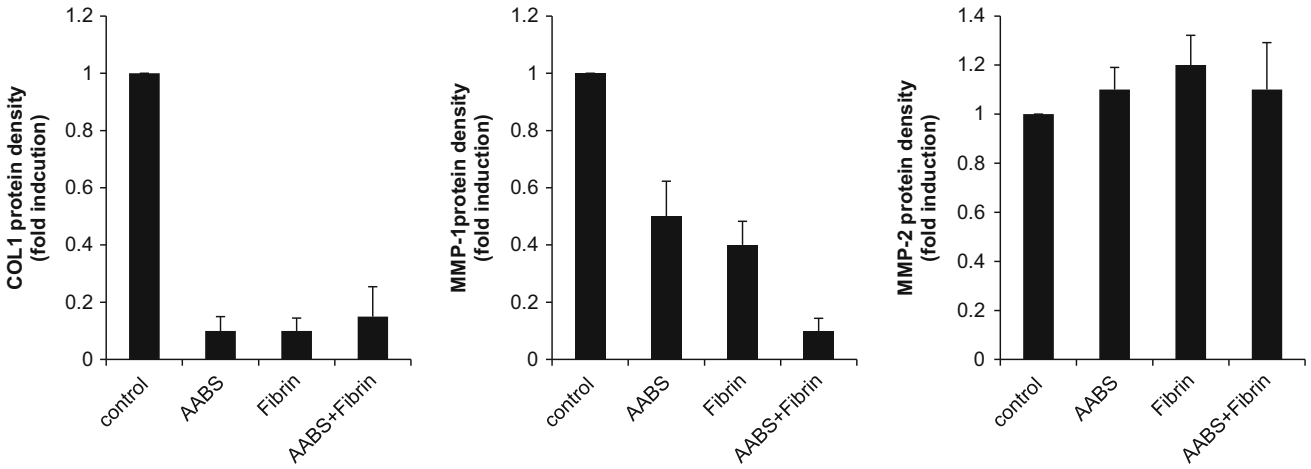

Fig. 6 Signal density of Western blot and zymography. The protein density of type I collagen and MMP-1 was lower in the experimental groups than in the control group ($p < 0.05$). The protein density of MMP-2 was not significantly different between the control and experimental groups ($p > 0.05$)

Collagen deposition is a decisive process during capsule formation. Type 3 collagen has less crosslinking than collagen type 1; hence, it has more elasticity than the latter [31]. Type 1 collagen is found in more rigid tissues, whereas type 3 collagen is found in more elastic tissues [32]. During scar formation, type 3 collagen is converted to type 1 collagen. Analogous to wound healing, the conversion of type 3 collagen into type 1 collagen may be involved in the development of capsular contracture [33]. Thus, type 1 collagen-rich capsule may be involved in capsular contracture, prompting evaluation of this protein.

In this study, the mRNA expression and Western blot results were different from those obtained during the evaluation of capsular thickness. Similar to the capsular thickness evaluation, all experimental groups had significantly lower type 1 collagen mRNA levels than the control group, but showed no significant difference in type 1 collagen mRNA levels when compared to other experimental groups. Although no significant difference was observed between AABS-, fibrin-, and combined AABS and fibrin-treated groups, we observed a trend of lower type 1 collagen mRNA levels in the AABS-treated group compared to those in the other two experimental groups. Based on this finding and the results of capsular thickness, we concluded that treatment with AABS alone might be more effective than treatment with fibrin alone or in combination of AABS in reducing fibrosis around implants.

In this study, we analyzed MMP-1, MMP-2, and TIMP-2. In both mRNA expression and Western blot analyses, expression of MMP-1 showed a pattern that was similar to that of type 1 collagen. This result is thought to be reasonable and in accordance with type 1 collagen expression. A pathological accumulation of collagen is directly attributed to the dysregulation of MMP activity [34]. Thus, low expression of MMP-1 is probably due to reduced type 1 collagen in the experimental group. However, unlike the above-mentioned studies [22], MMP-2 and TIMP-2 expressions were not significantly different between all the groups. Previous studies of Ulrich et al. [22, 29] suggested that the expressions of TIMPs and MMPs might decrease with decreasing capsular thickness. However, the expressions of MMPs and TIMPs are regulated by multiple pathway, many of which are poorly understood [35, 36], and elevated TIMP-2 expression has been previously observed in a periprosthetic environment [37]. Hence, it is possible that AABS and fibrin are capable of reducing capsule formation around implants, but may not be strongly affected by the expression of TIMP-2 within tissues surrounding the implants. In addition, we evaluated the levels of MMP-9 and TIMP-1, but were unable to detect them. A study of MMPs and TIMPs distribution in mice demonstrated that they have different localizations depending on the type of tissue [38]. According to the study, MMP-2 is very abundant in the heart, lung, kidney, and muscle tissue, whereas MMP-9 is found in all tissues but is expressed at low levels. TIMP-2 was constitutively expressed at high levels in all tissues of adult mice, whereas the other three TIMPs demonstrated a more selective pattern in terms of their tissue distribution.

To our knowledge, no study comparing the effects of AABS, fibrin, and combined use of AABS in prevention of fibrosis has been conducted prior to this study. Also, this study used a more objective and quantitative method for analysis of capsular tissue around the implants. However, this was a basic study, which had some limitations. The process of fibrosis starts within a few days, but it becomes quiescent and tends to regress after a few months [39], so the evaluation of fibrosis needs a longer follow-up period.

Another limitation was the use of silicone chips instead of breast implants. Thus, we may expand the study in the future using silicone implants, extending the follow-up period, using more larger animals, and measuring the intracapsular pressure which was one of the important factors to evaluate the capsular contracture.

Conclusion

AABS is more effective in reducing capsular thickness compared with fibrin treatment in a white rat model.

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Conflict of interest The authors declare that they have no conflict of interest.

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