Haemostatic Fleece (TachoComb®) to Prevent Intrapleural Adhesions after Thoracotomy: A Rat Model

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- thoracic surgery
- TachoComb
- adhesion
- preclinical
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Abstract

Background: Postoperative adhesion is a complication common to all surgical subspecialties. TachoComb® is a collagen fleece with properties well suited to the prevention of adhesion. This preclinical study was performed to evaluate the efficacy and mechanism of action of TachoComb in the prevention of adhesion following pleural injury during thoracic surgery.

Methods: Rats (n = 72) were randomised to receive saline or TachoComb following pleural injury. The macroscopic severity of adhesion formation and histological changes were assessed following euthanasia at time points up to 28 weeks post-operation. Levels of the biochemical markers t-PA, PAI-1 and bFGF were measured in intrapleural lavage fluid.

Results: The severity of adhesion was lower in TachoComb-treated animals compared with control animals at all time points (mean adhesion score: 1.4 vs. 4 at week 28 post-operation; $p < 0.01$). Regeneration of the mesothelial cell stratum occurred faster in TachoComb-treated animals, and a significantly lower PAI-1 activity was observed (14.32 vs. 23.28 U/ml; $p < 0.01$).

Conclusions: TachoComb is effective in the prevention of adhesion following thoracic surgery, both by acting as a physical barrier and by inhibiting PAI-1 activity.

Introduction

Postoperative adhesion is a complication common to all surgical subspecialties. Pulmonary redo surgery for adhesion is often carried out following procedures for metastatic lung tumours, recurrent pulmonary tumours, and repetitive pneumothorax. Adhesion in this setting is liable to be severe, particularly when it occurs along the incision line in the intercostal parietal pleura. When a large area is affected, the dissection of adhesions is associated with the risk of serious complications, including lung damage, bleeding and infection. However, there have been few studies on the prevention of intrapleural adhesion following pulmonary surgery [1,2].

The main cause of postoperative adhesion is a deposition of fibrin, which may occur with mechanical injury, bacterial infection, dryness, chemical stimulation or local ischaemia [3–5]. Mesothelial cells normally contribute to the prevention of adhesion by the production of tissue plasminogen activators (t-PAs), which degrade fibrin deposits [6]. When tissue damage occurs, tumour necrosis factors (TNFs) are released from macrophages [7], which rapidly cause the damaged mesothelial and inflammatory cells to release type 1 plasminogen activator inhibitor (PAI-1) [8,9]. PAI-1 suppresses t-PA activity, leading to an increased risk of adhesion formation [10]. Basic fibroblast growth factor (bFGF), which is released from macrophages, is involved in the regeneration of pleural mesothelial cells from fibroblasts [11–14].

TachoComb® (Nycomed, Linz, Austria) is a collagen fleece coated with the fibrin sealant components fibrinogen, thrombin and aprotinin, and has distinct properties that are well suited to the prevention of adhesion [15–18]. The product is ready for immediate clinical use without any prior conditioning, and the elasticity of the collagen permits application to a wide variety of tissues, including the constantly expanding and contracting surface of the lung. Like other membranes used to prevent adhesion, TachoComb acts as a physical barrier to adhesion; however, unlike other membranes, TachoComb also promotes wound healing by means of its haemostatic agents. [19–24].

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We used the rat model to investigate the effectiveness of TachoComb in the prevention of adhesion following thoracic surgery and compared the outcomes when using only saline. The present study was performed not only to measure the occurrence of adhesions after the application of TachoComb, but also to elucidate the mechanism of action through an assessment of the biochemical markers t-PA, PAI-1, and bFGF.

Materials and Methods

This study of male Sprague-Dawley rats was conducted in compliance with the Guidelines for Laboratory Animal Experiments at the Sapporo Medical University School of Medicine, and in accordance with the Guidelines for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH publication no. 86 – 23; 1985).

Rats (n = 75) were randomised into three groups: group 1 (n = 36) received saline post-incision, group 2 (n = 36) was treated with haemostatic fleece (TachoComb) post-incision and group 3 consisted of control rats (n = 3) which were not operated on, representing the normal state of the chest cavity.

The rats in groups 1 and 2 were lightly anaesthetised with ether, intubated endotracheally with a 2.5-inch, 14 gauge angiographic catheter, and connected to a rodent ventilator (Harvard Apparatus 683; South Natick, MA, USA), which was adjusted to maintain ventilatory values in the normal range. Anaesthesia was maintained with 0.5 – 2.0% halothane and rats were prepared for left thoracotomy. The rats were placed in the right lateral decubitus position and an incision made 20 mm from the intercostal muscles and the pleural membranes along the costal line from the fifth intercostal space.

Mechanical, chemical and ischaemic injuries were inflicted as described by Tanaka et al. [25]. The subcostal parietal pleura on both sides of the thoracic incision was abraded with a bone scaler; the surface of the left lung was abraded five times with gauze soaked in 0.1 ml of iodine solution; and blood flow in the proximal (dorsal) and distal (ventral) parts of the intercostal artery on both sides of the thoracic incision was completely shut off by electric cautery to produce ischaemia in the chest wall.

In the rats in group 1, 1.0 ml of saline was dropped into the pleural cavity. In the rats in group 2, a 15 × 25 mm area of TachoComb was affixed to the surface of the lung after abrasion and pressed down for 5 minutes. The chest wall was then closed.

Euthanasia and necroscopy were performed on the rats in groups 1 and 2 at 24 hours (n = 6 for each group), on day 3 (n = 5), day 5 (n = 5), day 7 (n = 5), at 4 weeks (n = 5), 16 weeks (n = 5), and 28 weeks (n = 5) postoperatively. The same procedure was followed for the rats in group 3 (time: not applicable).

Post-euthanasia observations

All macroscopic and pathohistological observations were performed by a pathologist who was blinded to the interventions.

Macroscopic examination

To evaluate the severity of intrapleural adhesion in rats in groups 1 and 2, a thoracotomy from the eighth or ninth intercostal space was carried out following euthanasia at 24 hours, on day 7, at 4 weeks, 16 weeks, and 28 weeks postoperatively. The length of the adhesion was measured as the maximum length of adhesion in the lung along the first intercostal incision. The severity of adhesion formation was classified as grade 1 – 4 (1, no adhesion; 2, mild adhesion, which can be separated bluntly; 3, moderate adhesion, which partially requires sharp dissection; and 4, severe adhesion, which must be entirely separated by sharp dissection) [25].

Pathohistological examination

The chest wall, including the third to eighth ribs and the adhering lung tissues, was resected in total for pathohistological evaluation of intrapleural adhesion formation following euthanasia at 24 hours, on day 7, at 4 weeks, 16 weeks, and 28 weeks after treatment.

The excised chest wall was fixed with a neutral buffer solution of 10% formalin and decalcified with Plank-Rychlo solution (0.3 M aluminium chloride, 3% hydrogen chloride, and 5% formic acid; Plank and Rychlo 1952) [26]. Three segments, cut at intervals of about 5 mm vertically to the ribs, were embedded in paraffin and stained with haematoxylin/eosin. Light microscopy was used to examine the segment from each rat showing the most severe inflammation, as well as the parietal pleura immediately under the cranial and caudal portions of the first and second ribs in the intercostal pleural incision [25].

Cellular changes in the parietal pleura of rats in groups 1 and 2 were graded in accordance with the criteria described by Tanaka et al. [25]. The proliferation of mesothelial cells was graded 1 – 4 according to the extent of coverage of the pleural surface with mesothelial cells (1, 100%; 2, ≥ 50%; 3, ≤ 50%; 4, 0%). The infiltration of mononuclear inflammatory cells (except for macrophages) and macrophages alone in the collagen stratum below the pleural surface and the adhering lung tissues were graded separately from 1 to 3 (1, almost none [mild]; 2, < 100 [moderate]; 3, ≥ 100 [severe]).

Determination of activities of t-PA and PAI-1

The activity of t-PA and PAI-1 in intrapleural lavage fluid (ILF) was measured following euthanasia in control rats (group 3), and at 24 hours postoperatively in groups 1 and 2. The concentration of bFGF in ILF was also measured in group 3, and at 24 hours and on days 3, 5, and 7 in groups 1 and 2.

Saline (8.0 ml) was injected into the thoracic cavity from a small incision in the ninth intercostal site. A 4.5 ml sample of ILF was taken and 0.2 ml of 3.8% sodium citrate solution added. The sample was agitated five to six times, and centrifuged at 3000 rpm and 4 °C for 10 minutes.

To measure t-PA activity, 0.5 ml of supernatant was added to 4.5 ml of distilled water, and 0.1 ml of 0.5% acetate was added. The chromogenic synthetic substrate method was used to measure t-PA activity [27,28] (Chromolize™ t-PA Assay Kit; Biopool International, Inc., Ventura, CA, USA; lower limit of determination sensitivity: 0.5 IU/ml). PAI-1 activity was measured in 0.5 ml of supernatant by the chromogenic synthetic substrate method [28,29] (Spectrolyse®/pL PAI Chromogenic Assay Kit; Biopool International, Inc., lower limit of detection: 1.0 U/ml). The concentration of bFGF was measured in 1 ml of supernatant by enzyme-linked immunosorbent assay (ELISA; [30,31] Quantikine® FGF Basic Immunoassay Kit; R&D Systems, Inc., Minneapolis, USA; minimum detectable concentration: 10 pg/ml). All samples were stored at – 80 °C until assayed.

Statistical methods

Mann-Whitney U test (nonparametric, two-tailed) was used for comparisons of groups 1 and 2. All tests were performed at the 5% level of significance.

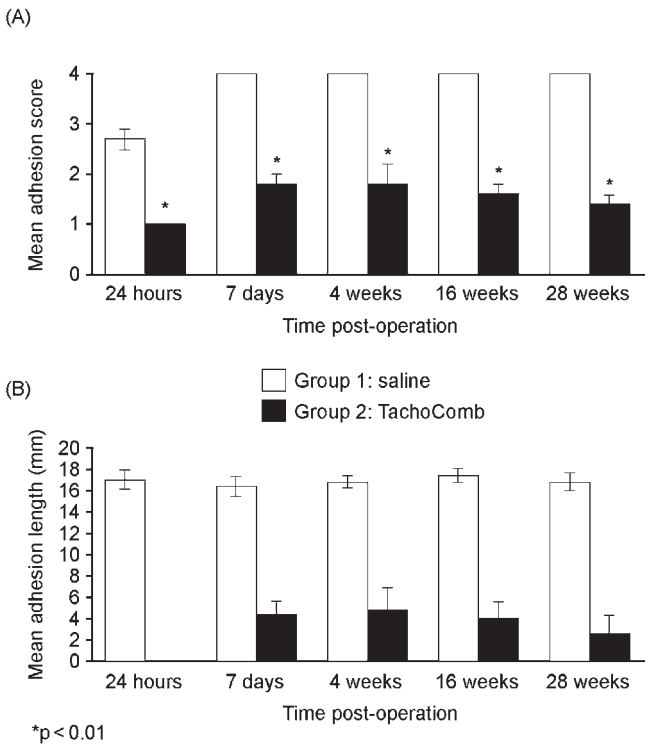

Fig. 1 A and **B** Post-euthanasia macroscopic adhesion. **A** Mean adhesion score (where error bars are absent, standard error is zero), and **B** mean adhesion length.

Results

At every time point, the mean adhesion score was significantly lower in rats treated with haemostatic fleece (group 2) than in those given saline (group 1) (**Fig. 1 A**; $p < 0.01$ at all time points). Severe adhesion (grade 4) was detected in all rats in group 1 at all time points from day 7 (**Fig. 1 A**). In contrast, adhesion was either absent or mild in all animals in group 2 at all time points (**Fig. 1 A**), with the exception of one rat that presented with moderate adhesion (grade 3) at week 4. Correspondingly, the mean adhesion length was significantly shorter in group 2 vs. group 1 (**Fig. 1 B**; $p < 0.05$ at all time points). Sixteen weeks after treatment, a small quantity of residual haemostatic fleece was observed with scar tissue in group 2, but by week 28 there was only negligible macroscopic evidence of haemostatic fleece (**Fig. 2**).

Pathohistological investigation of sections of the parietal pleura indicated successful inhibition of adhesion formation and reduced inflammation in group 2 compared with group 1. A greater regeneration of the mesothelial cell stratum was observed in group 2 (**Fig. 3 A**) compared with group 1 (**Fig. 3 B**) on day 7 postoperatively. Accordingly, a lower mesothelial proliferation score was observed in group 2 at this time (**Table 1**; $p = 0.009$). The number of mononuclear inflammatory cells (excluding macrophages) was significantly higher in group 1 than in group 2 (**Table 1**; $p = 0.0163$). Conversely, there was greater infiltration of macrophages in group 2 (**Table 1**; $p = 0.009$). Four weeks after treatment, rats in group 2 exhibited proliferation of fibroblasts and macrophages, a conglomeration of plasma cells, and formation of granulomatous tissue, with the haemostatic fleece becoming thinner and coarser as a result of phagocytosis and absorption (**Fig. 3 C**). By week 16, the level of TachoComb remaining in group 2 was reduced at histological levels (**Fig. 3 D**).

Twenty-four hours after treatment, a significantly lower PAI-1 activity was detected in group 2 than in group 1 (14.32 vs. 23.28 U/ml; $p < 0.01$). PAI-1 activity was below the minimum detectable level in the control group (group 3). Likewise, t-PA activity was lower than the minimum detectable level in all rats assessed. In terms of bFGF levels, there was no significant difference between groups 1 and 2 at any time point (**Table 2**). The concentration of bFGF was below the level of detection in group 3 rats.

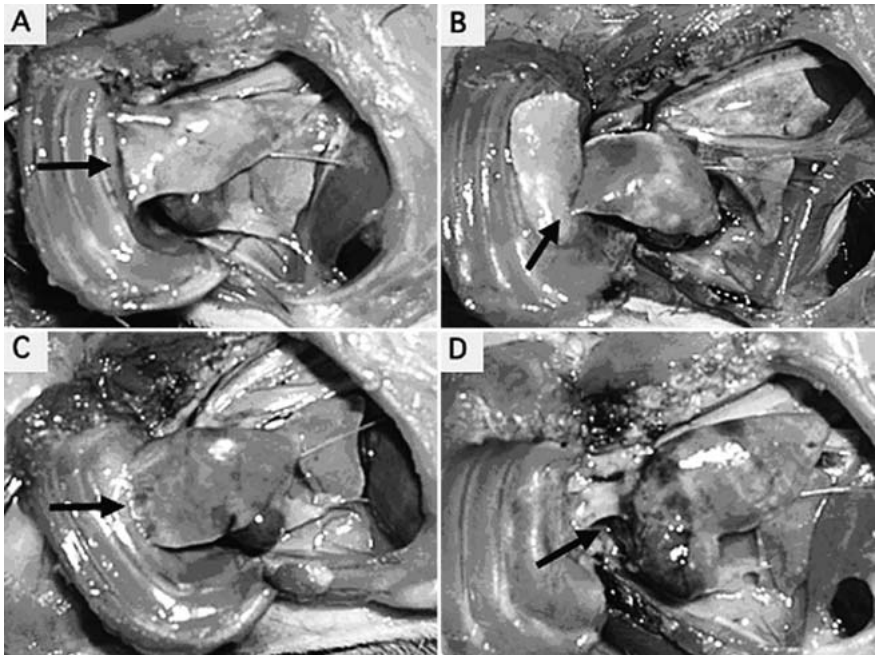

Fig. 2 A to **D** Post-euthanasia macroscopic findings from the study (all times are posttreatment). **A** Severe adhesion (grade 4) between the lung surface and parietal pleura on day 7 in an animal treated with saline. **B** Haemostatic fleece partially fixed onto the lung surface on day 7 in the presence of mild adhesion (grade 2). **C** Severe adhesion (grade 4) between the lung surface and parietal pleura in week 16 in an animal treated with saline. **D** No adhesion (grade 1), residual haemostatic fleece and scar tissue between the lung surface and parietal pleura in week 16.

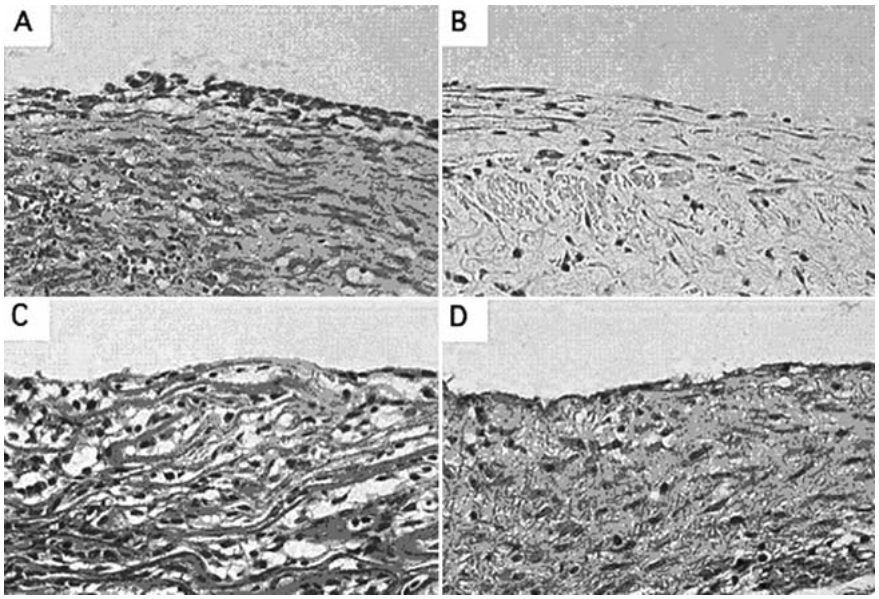

Fig. 3 A to **D** Post-euthanasia histological findings from the study (all times are posttreatment); all images were taken at a magnification of × 200 (stain: haematoxylin/eosin). **A** Regenerated mesothelial cell stratum on day 7 in an animal treated with haemostatic fleece. **B** Incomplete mesothelial cell stratum on day 7 in an animal treated with saline. **C** Infiltration of inflammatory cells mainly consisting of plasma cells and lymphocytes in week 4 in an animal treated with haemostatic fleece. The fleece is thinner and coarser and the mesothelial cell stratum is partially regenerated. **D** Almost complete substitution of the haemostatic fleece with fibrous components at week 16 with few inflammatory cells present.

Table 1 Cellular findings in the parietal pleura on day 7 post-operation

	Group 1: saline	Group 2: TachoComb	*p* value (group 1 vs. group 2)
Mesothelial proliferation score	3.5 ± 0.2	2.3 ± 0.2	0.009
Infiltration of monocytes score	2.3 ± 0.1	1.6 ± 0.1	0.0163
Infiltration of macrophages score	1.2 ± 0.1	2.4 ± 0.2	0.009

Mean scores ± standard error are shown

Table 2 Concentration of bFGF (pg/ml ± standard error) in intrapleural lavage fluid supernatant

Time post-operation (days)	Group 1: saline	Group 2: TachoComb	*p* value (group 1 vs. group 2)
1	25.7 ± 2.2	22.3 ± 1.5	0.3785
3	22.0 ± 1.5	19.2 ± 1.5	0.6761
5	25.6 ± 5.8	21.4 ± 1.5	0.6761
7	58.8 ± 19.3	43.4 ± 1.5	0.4647

bFGF: basic fibroblast growth factor

Discussion

This is the first study to demonstrate that TachoComb can significantly reduce the risk and severity of adhesion formation following thoracic surgery. TachoComb acts not only as a physical barrier to adhesion, but also promotes tissue repair and biochemically inhibits adhesion at the site of trauma. TachoComb possesses the membrane flexibility needed to accommodate the constant expansion and contraction of the lung while providing effective sealing of the tissue.

These findings are consistent with previous studies showing that TachoComb may be effective in reducing adhesions following gynaecological surgery, with a reported reduction in adhesion following surgery for the correction of conditions causing infertility in women [18,32]. Furthermore, preclinical studies in a rabbit model have suggested that TachoComb elicits a significant reduction in the rate of adhesion following suturing of the uterine horn or the infliction of mechanical and chemical injuries during laparotomy [17,33].

Macroscopic observation in the present study demonstrated that adhesion was absent or mild in all but one of the animals treated with TachoComb. In contrast, severe adhesion was observed in all rats treated with saline, which persisted throughout the study. As well as demonstrating the effectiveness of TachoComb, these results show that the model used in this study reliably induced adhesion.

It takes 7 – 8 days for regeneration of the mesothelial cell stratum to be completed following tissue damage, regardless of the extent of mesothelial loss [11,12]. Adhesions may form throughout this time. The goal of biodegradable membranes is to provide a physical barrier to separate the adjacent parietal pleura and thereby to reduce adhesion formation, with degradation of the material thereafter. In this study, the quantity of residual TachoComb was greatly reduced by week 16 and by week 28, there was no macroscopic evidence of the product. The decomposition and absorption rates of TachoComb are dependent upon the site of application and the quantity used – differences between species may also be expected. In previous animal studies, TachoComb was reported to be degraded within 3 months in the canine liver and brain and in the lapine kidney, and in 16 – 20 weeks in the rat liver [34,35]. A study of TachoComb in the human cervix reported its degradation within 6 weeks [36].

Pathohistological findings from this study revealed a beneficial cellular response to the application of TachoComb. Mesothelial cells regenerated more rapidly in rats treated with TachoComb than in those receiving saline, demonstrating a significant inhibition of adhesion. Furthermore, the lower levels of inflammatory mononuclear cells suggest a greatly decreased inflammatory response among rats treated with TachoComb. Greater numbers of macrophages were observed in the TachoComb group, which is very likely related to the degradation process (phagocytosis). It has been suggested that the proliferation of fibroblasts during

the healing process is accelerated and controlled by macrophages [14].

It has been suggested that dissolution of fibrin (and prevention of adhesion) in the normal mesothelial cell stratum is maintained by low-level t-PA activity, and that a rise in PAI-1 levels can inhibit t-PA activity, thus allowing adhesions to form [10]. In this study, postoperative PAI-1 activity was significantly lower in rats treated with TachoComb compared with rats treated with saline, which would have contributed to the prevention of adhesion in the TachoComb group. The bFGF concentration in ILF was expected to become high in rats treated with TachoComb, due to the likelihood of a foreign-body reaction and the regeneration of pleural mesothelial cells. However, no significant difference between rats treated with TachoComb or saline was observed in terms of bFGF levels. This may be attributable to bFGF being released for the tissue repair process (in both groups), thus masking the effect of TachoComb.

TachoComb was originally used to adhere or enclose tissues. However, some physicians suspect that TachoComb is more likely to cause postsurgical adhesion because of its strong haemostatic effect and other membranes have been often used to avoid adhesion. But there have been few studies on their use following thoracic surgery. Tanaka et al. showed that a hyaluronic acid-based membrane reduced the severity of adhesion following thoracic surgery in the same rat model as in the present study [25]. Other preclinical studies, using a canine model, demonstrated that other membranes, composed of materials such as hyaluronic acid and polyethylene glycol/polylactic acid, reduced the severity of pericardial adhesion following cardiac operations [37,38]. TachoComb has numerous advantages over other membranes as a material to prevent postsurgical adhesion. Nonabsorbent membranes, such as polytetrafluoroethylene (PTFE), require suturing to the tissue, as well as subsequent intervention to remove the material after healing [39]. In contrast, TachoComb is biodegradable (this study and others have shown that it degrades over a period of 6 – 20 weeks), negating the need for removal of the material after its application. TachoComb also does not require suturing to the application area, due to the inclusion of fibrin sealant components, which facilitates bonding to the application site. Other biodegradable agents are available, such as a cellulose-based membrane (Interceed; Ethicon, Hamburg, Germany), but these have shown limited effectiveness which was attributed to rapid degradation of the material and foreign-body reactions [39,40]. TachoComb did not elicit any detrimental foreign-body reactions in this study, with little or no inflammation observed. No major drawbacks were reported with a sodium hyaluronate-based bioresorbable membrane: in an initial clinical study, a reduction in the incidence and severity of adhesion formation in patients undergoing abdominal and pelvic surgery was reported [41,42]. Nevertheless, this material does not possess a dual mechanism of action. TachoComb not only acts as a physical barrier to adhesion, but also promotes the wound healing process. There does not appear to be any good reason to use TachoComb for haemostasis and other materials for the prevention of adhesion. From an economic point of view, nowadays, medical budgets tend to be fairly restrictive, especially for surgical interventions. TachoComb provides new surgical options for time-consuming operations with complex bleeding, reducing the operating times, the length of stay in the normal ward or ICU, and saving about half of the costs [43]. This study additionally suggests that TachoComb might also save the cost of additional materials used to prevent adhesion.

Conclusions

The results of this study demonstrate that TachoComb can serve as a protective physical barrier to adhesion at both macroscopic and histological levels, with a significantly decreased incidence and severity of adhesion compared with saline. TachoComb degenerates over time, so that there was little macroscopically visible residual material in week 16, and none in week 28 postoperatively. The presence of TachoComb facilitated the rapid regeneration of the mesothelial cell stratum, and was accompanied by a decrease in mononuclear inflammatory cells. TachoComb also prevented an increase in PAI-1 activity, which likely contributed to the inhibition of adhesion.

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