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Sporopollenin-based material for prevention of postoperative adhesions: a murine study

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Purpose: This study was performed to evaluate the antiadhesive effect and safety of a novel adhesion barrier device (ABD) in comparison to other commercially available anti-adhesion products.
Methods: A 4-arm, controlled, blinded, experimental, and murine model study design was used. Forty male Sprague Dawley rats were randomly allocated to Interceed, Seprafilm, ABD, and control groups (n = 10/group). Abdominal cavity trauma was induced in all rats. Interceed, Seprafilm, or the ABD were applied to the injury site of each rat according to their respective groups, the control group received no intervention.
Results: Twenty-one days after the operation, surgical adhesion severity and area scores were significantly reduced in the Interceed, Seprafilm, and ABD groups compared to the control group ($P = 0.016$, $P < 0.001$, $P < 0.001$, respectively), and in the ABD group compared to the Interceed group ($P = 0.036$). No significant difference was observed between the ABD and Seprafilm groups ($P = 0.070$). Additionally, in the ABD group, no remnants of the ABD were observed at the injury site, and no hematological abnormalities were present.
Conclusion: The ABD has the potential to improve postsurgical peritoneal adhesions compared to Interceed and has comparable effectiveness compared to Seprafilm. The ABD may be a valuable option to reduce surgical failure. Further studies in human subjects are warranted to determine the clinical application and safety of the ABD for commercialization.
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Key Words: Biopolymers, Immunomodulation, Pollen, Sporopollenin, Tissue adhesions

INTRODUCTION

Postsurgical adhesions, fibrous bands of scar tissue forming between adjacent tissues or organs, following surgical trauma, are a persistent issue across clinical domains, making their mitigation an ongoing challenge. This complication can

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directly or indirectly cause chronic pain and dysfunction and may necessitate further surgeries, impacting quality of life [1]. Despite advancements in surgical techniques, adhesions occur in 50%–90% of surgeries, irrespective of procedure or anatomical location. In particular, the rate of postoperative adhesion is 70%–90% following laparotomy [2], 6%–17% following cardiac surgery [3], more than 50% following thyroid surgery [4], and over 90% following gynecological surgery [5]. In the United States, adhesion-related complications add nearly 1 million inpatient care days annually, with a healthcare economic burden that surpasses $2.5 billion annually, highlighting the urgent need for preventive postoperative adhesion solutions.

Various adhesion barriers, made from natural or synthetic products, have been utilized since the 19th century to minimize internal scarring following surgery by separating the internal tissues and organs during the healing process. Currently, resorbable barrier films are the most popular barrier products because they do not require a second surgical procedure to remove them. Moreover, these products function solely as physical barriers without pharmacological, immunological, or metabolic effects. Major commercially available adhesion barriers for abdominal and pelvic adhesions include Interceed (Gynecare, Ethicon, Johnson & Johnson Company) and Seprafilm (Baxter Healthcare). However, these products do have their drawbacks. Interceed is contraindicated for surgeries involving blood fields [6] because it may lead to the promotion of fibrin deposition in the presence of blood, which leads to adhesion formation [7]. Seprafilm consists of modified hyaluronic acid and carboxymethylcellulose, rendering it brittle and prone to adherence to moist surfaces, including surrounding tissues and surgical instruments. Moreover, given its brittle nature, Seprafilm cannot be introduced through a trocar, meaning it cannot be used during laparoscopic procedures. A viable alternative that addresses these limitations is needed.

In the past 4 years, several scientific investigations have reported that surgical trauma-triggered immune responses can disrupt the intricate balance between pro- and anti-inflammatory factors necessary for optimal tissue healing, leading to the formation of adhesions [1-3,5,8]. Our recent understanding of the central role of inflammation in the formation of postsurgical adhesions provided a unique direction for the development of a targeted intervention capable of managing and preventing postsurgical adhesions at their source.

Plant pollen, a natural biopolymer extracted from flower pollen, has emerged as an innovative biomaterial with diverse medical uses [9]. The microcapsule bilayer structure of pollen protects its internal contents from environmental stresses like dehydration and hydrolysis, and the hard exine outer layer, composed of sporopollenin, is resistant to both acids and alkalis [10]. In addition, pollen has many therapeutic properties and can stimulate the immune system, modulating the immune response [11]. We created a resorbable adhesion barrier device (ABD) with potential material-mediated immunomodulating properties using natural biocompatible substances, particularly sporopollenin. Here we report an *in vivo* study to evaluate the antiadhesive effect of the ABD compared to 2 other commercialized antiadhesive products (Interceed and Seprafilm).

METHODS

Ethics statement

All protocols in this study were approved by the Institutional Animal Care and Usage Committee (IACUC) at Tufts Comparative Medicine Services, Tufts Medical Center, Tufts University (permit No. B2020-53), in compliance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication no.85-23, revised 1996). The authors complied with the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines.

Materials

Material preparation

The ABD is comprised of several materials, including dextran sulfate sodium salt Mw ~40,000 (Alfa Aesar catalogue code: J63606, Thermo Scientific), polyethylene glycol (PEG) 1500 (catalogue code: 81210, Sigma Aldrich), sodium carboxymethyl cellulose (CMC) Mw ~90,000 (catalogue code: 419273, Sigma Aldrich), citric acid (CA; catalogue code: 251275, Sigma Aldrich), potassium hydroxide (KOH; Vetec catalogue code: V800322, Sigma Aldrich), and sporopollenin.

Sporopollenin was extracted from defatted sunflower pollen powder, *Helianthus annuus*, obtained from GREER Laboratories, Inc. The extraction process involved an alkaline hydrolysis procedure. Initially, 2 g of defatted sunflower pollen was suspended in 20 mL of 10% w/v KOH solution and heated for 2 hours at 80 °C with continuous stirring. The pollen was then isolated through filtration and rinsed multiple times with 10% w/v KOH solution. The rinsed pollen was centrifuged at 4,000 revolutions per minute (rpm) for 15 minutes, discarding the supernatant each time, until it reached a suspension pH of about 7 to 8. The final concentration of the resulting sporopollenin microgel was mixed with the other materials according to the composition specified in Table 1.

The weight percentage of the sporopollenin was fixed at 7.5% with respect to the total weight of the polymer (CMC, PEG, CA, dextran). The amount of sporopollenin microgel blend varied in terms of volume because the concentration of the final sporopollenin microgel mixture varied depending on the washing process. The final solid (CMC, PEG, CA, dextran, sporopollenin) concentration of the microgel was kept constant at 49.5 mg/mL to fix the viscosity of the casting solution. The final solution was topped up with deionized water to achieve a

Table 1. Composition of the adhesion barrier device

Material	Weight ratio	Weight (mg)	Volume (mL)	Concentration (mg/mL)
CMC	4.7	1,469.20		25.8
PEG	1.4	437.65		7.7
CA	1	312.6		5.5
Dextran	1.3	406.4		7.1
Total polymer		2,625.85		49.5
Sporopollenin		197.64		3.7
Sporopollenin microgel			6.984	
Total solution			57.073	
DI water to be added			50.089	

CMC, carboxymethyl cellulose; PEG, polyethylene glycol; CA, citric acid; DI, deionized water.

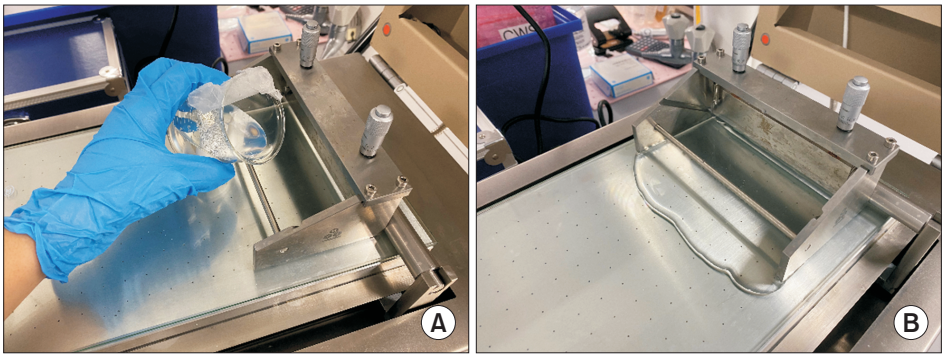

Fig. 1. Fabrication process for adhesion barrier device. (A) Casting of 7.5% wt sporopollenin solution onto automatic sheet film coater. (B) Consistent film thickness of 0.07 mm was achieved by pushing the doctor blade.

final concentration of 49.5 mg/mL as a clear and viscous liquid.

Adhesion barrier device fabrication

The viscous liquid was cast using an automatic film coater with a heatable vacuum bed and a 250-mm doctor blade (MSK-AFA-II-VC-FH, MTI Corp.) (Fig. 1). The final solution cast was about 57 mL based on the material composition shown in Table 1. The amount of solution was roughly sufficient for 1 casting at a height of about 3 mm. After casting, a removable glass substrate with a casted solution film was placed in an oven at 50 °C for 24 hours to dry. After drying, the film became pale yellow in color and was easily peeled from the glass substrate. Thus, the ABD in the form of a stand-alone film was obtained.

Swelling and viscoelastic properties

A swelling test was conducted to compare the ABD (thickness, 0.07 mm) with Seprafilm (thickness, 0.05 mm). Discs with a diameter of 6 mm (hole-punched size) were cut from each film and immersed separately in 20-mL vials containing 8 mL of phosphate-buffered saline (PBS) with a pH of approximately 7.4. The vials were then incubated at 37 °C for up to 96 hours or dissolution, whichever occurred first. Volumetric swelling capacity (%) based on the diameter and thickness of the disks was monitored at 0, 1, 2, 24, 48, and 96 hours. Three samples of the ABD and 3 samples of Seprafilm were analyzed and data points for volumetric swelling capacity were plotted for 0, 1, 2, 24, 48, and 96 hours.

For tensile testing, rectangular pieces, measuring 15 × 100 mm with a thickness of 0.07 mm, were cut from ABD film and Seprafilm. The stress-strain and tensile strengths were measured using a universal testing machine (H5KT, Tinius-Olsen) at a feed rate of 1 mm/min with a force of 50 N. The elastic modulus of each film was calculated from the slope of the linear region (0.1%–4% strain) of the stress-strain curve. The toughness of each film was calculated from the area under the stress-strain curve. Three samples of ABD film and 3 samples of Seprafilm were analyzed separately.

Phenolic extract

A methanol/water extraction method was utilized for the phenolic extraction of sporopollenin [12]. First, 80% methanol was added to cleaned sporopollenin and stirred for 1 hour. The solution was then centrifuged at 5,000 rpm for 10 minutes to obtain the supernatant. Phenolic absorption peaks were observed at 280 nm using ultraviolet-visible (UV-VIS) absorption spectroscopy (Cary 60 UV-VIS spectrophotometer, Agilent Technologies). A phenolic content calibration graph was plotted based on the methanol/water extracted from different concentrations of cleaned sporopollenin.

Blinded animal study

Preclinical animal studies were conducted at Tufts Medical

Center, University of Tufts, to assess the efficacy of the ABD in preventing postsurgical abdominal adhesion formation compared with 2 other antiadhesive barrier products, Seprafilm and Interceed, and a control group.

Forty 8-week-old male Sprague Dawley rats weighing between 230 and 280 g were obtained from Tufts Medical Center for this study. We have chosen only male rats in this study to reduce potential variables due to sex differences. The animals were housed for 1 week prior to surgery to acclimatize to the new environment with a 12-hour light/dark cycle. Rats were housed in pairs in standard polycarbonate cages with stainless steel mesh lids. Clean sterilized corn cob was provided as bedding. The rats were fed *ad libitum* with standard laboratory animal feed and ultraviolet-sterilized drinking water throughout the acclimatization and experimental period. The feed, drinking water, and bedding were analyzed periodically for fungal and microbial contamination.

Each rat was randomly assigned a number and allocated to 1 of 4 groups: Interceed, Seprafilm, ABD, or control (n = 10/group). Interceed, Seprafilm, and ABD rats were assigned respective adhesion barrier interventions, and the control group received no adhesion barrier.

In all 40 rats, trauma was induced in the cecum and adjacent tissue of the abdominal wall following procedures outlined in the IACUC Animal Protocol. We have chosen the anatomic location in the cecum and adjacent abdominal wall because they are predictable in extent and severity and are easily measurable [6]. The standardized process involved a 60-mm midline laparotomy incision. Trauma to the surface of the cecum was induced by abrasion with surgical gauze, while trauma to the wall of the opposing parietal peritoneum, including a portion of the underlying muscle, was produced by excising a 2 × 2 cm area using a sterile scalpel. Subsequently, Interceed, Seprafilm, and ABD barriers were applied to the respective groups (Fig. 2). The control group received no adhesion barrier intervention. The midline incision was closed. All surgical procedures

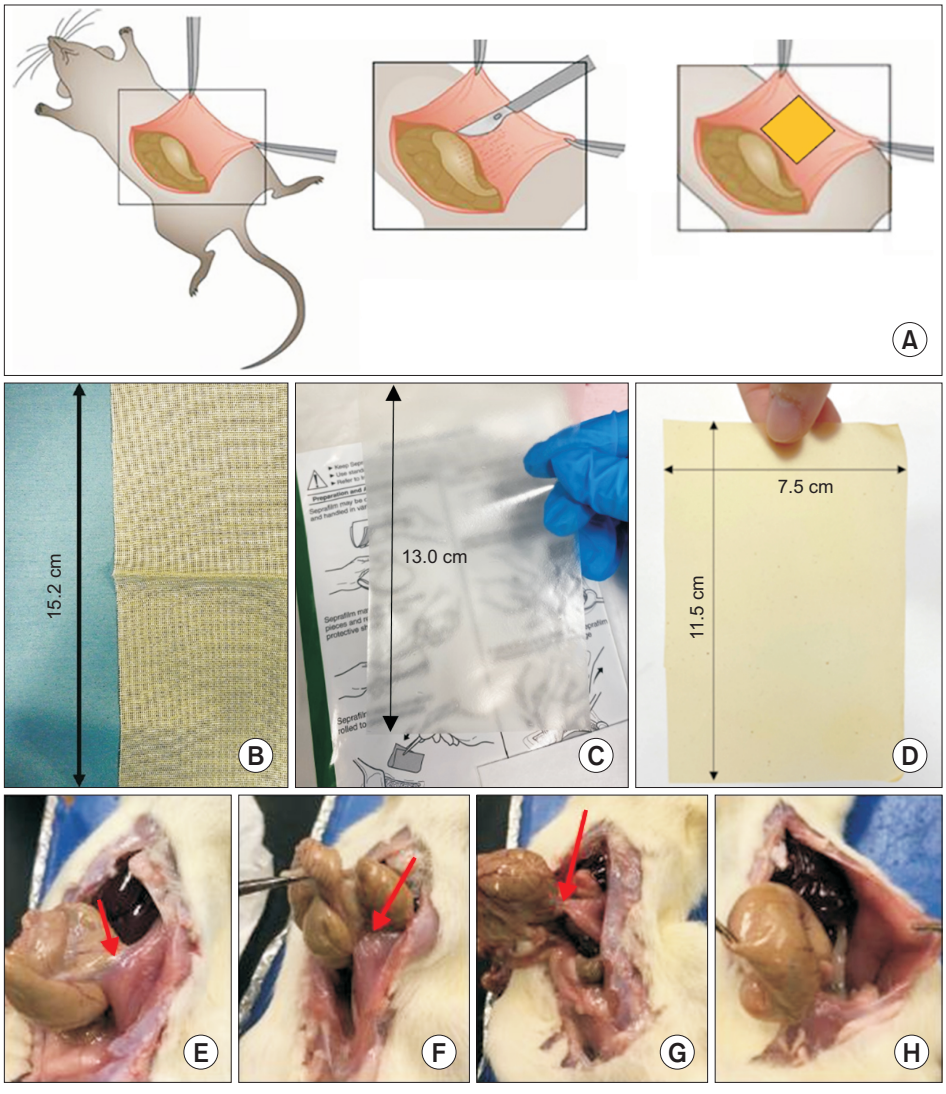

Fig. 2. Animal studies to investigate the efficacy of the adhesion barrier device (ABD) and representative images of adhesions 21 days after injury. (A) Laparotomy was performed in rats (n = 40) followed by standardized trauma inflicted to the cecum and adjacent abdominal wall (2 × 2 cm). Three adhesion barriers—(B) Interceed (Gynecare, Ethicon, Johnson & Johnson Company), (C) Seprafilm (Baxter Healthcare), and (D) ABD—each cut to a size of 3 × 3 cm, were applied to 3 respective groups (n = 10/group), excluding the control group (n = 10), which received no intervention, and the midline incision was closed. After 21 days after injury, the animals were sacrificed, and the abdominal cavity was opened via a 60-mm midline incision. The severity and area of adhesion between the cecum and abdominal wall were evaluated. Red arrows in the figures highlight the formation of adhesion. (E) Control, (F) Interceed, (G) Seprafilm, and (H) ABD representative images.

were carried out by a researcher who was blinded to group assignment.

Evaluation of adhesions

Twenty-one days after surgery, all rats were euthanized with excessive sodium pentobarbital (120 mg/kg). The abdominal cavity was opened via a 60-mm midline incision (Fig. 2). A researcher who was blinded to group allocation evaluated and scored the severity and area of adhesion between the cecum and abdominal wall according to the widely used Adhesion Severity and Adhesion Area Scoring Scheme (Table 2) [13].

Statistical analyses of adhesions

Adhesion severity and area scores were compared using 1-tailed Student t-tests, and correlations between adhesion severity and area were analyzed using Spearman rank correlation analysis. For all outcome measures, P-values <0.05 were considered statistically significant.

Histological examination

After euthanasia by carbon dioxide asphyxiation, sections of the abdominal wall from rats from the ABD group were sent for histological analysis in formalin. Tissue was trimmed, cassetted, sectioned at 5 microns, and stained with H&E by the Tufts Animal Histology Core Facility.

Blood chemistry

Prior to injury (Day 0), blood analysis was conducted on 5 randomly selected rats from each of the control group and ABD group. For baseline blood analysis, 1 mL of blood was drawn from the tail vein of each rat. Twenty-one days after the operation, bloodwork was repeated on the same 5 rats in the control group and ABD group. For follow-up blood analysis, 6 mL of blood was obtained via cardiac puncture. Ethylenediaminetetraacetic acid tubes and red-top serum collection tubes were used for blood collection. Blood work was analyzed by a third-party laboratory (IDEXX BioAnalytics) under blinded conditions.

Table 2. Adhesion Severity and Adhesion Area Scoring Scheme [13]

Score	Description	
	Adhesion Severity	Adhesion Area
0	No adhesions	No adhesions
1	Thin filmy adhesion	<25% of initial injured area
2	More than one thin adhesion	25%–50% of initial injured area
3	Thick adhesion with focal point	50%–70% of initial injured area
4	Thick adhesion with planar attachment	75%–100% of initial injured area

Table 3. Hematology and blood chemistry (specimen: anticoagulated whole blood; serum)

Variable	Control group										ABD group									
Time	Preoperation					POD 21					Preoperation					POD 21				
Rat ID	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Neutrophil (%)	18.1	22.1	14.4	12.9	13.9	10.4	14.8	13.0	14.0	15.5	19.5	21.0	14.8	13.9	10.5	14.4	9.8	13.8	10.3	24.0
Neutrophil (/μL)	2,498	3,249	3,542	2,141	2,627	1,508	1,939	2,366	2,548	3,271	2,477	3,219	3,542	2,141	2,521	2,117	941	2,277	1,298	2880
Reticulocyte (%)	4.5	5.9	5.9	5.3	6.5	3.0	4.0	3.6	4.0	3.6	5.7	5.6	5.5	4.3	5.5	4.1	3.5	5.2	3.5	4.1
WBC (K/μL)	13.8	14.7	24.6	16.6	18.9	14.5	13.1	18.2	18.2	21.1	14.8	16.8	20.7	13.3	19.3	14.7	9.6	16.5	12.6	12.0
Absolute reticulocyte (K/μL)	312	428	444	403	412	241	314	282	326	267	325	338	354	434	422	335	280	366	294	311
Band (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Band (/μL)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
RBC (M/μL)	6.93	7.25	7.53	7.60	6.34	8.03	7.86	7.82	8.16	7.41	6.38	7.75	6.53	6.88	6.94	8.18	8.00	7.03	8.40	7.59
Hemoglobin (g/dL)	14.0	14.7	15.1	15.1	14.0	14.9	14.6	14.9	15.2	14.8	14.5	14.9	15.1	15.5	15.0	15.4	15.3	14.0	15.9	14.6
Lymphocyte (/μL)	10,336	10,584	19,852	13,595	15,120	12,166	10,624	15,324	14,542	16,775	13,460	12,584	16,856	14,595	14,460	11,878	8,198	13,398	10,521	8,700
Lymphocytes (%)	74.9	72.0	80.7	81.9	80.0	83.9	81.1	84.2	79.9	79.5	84.2	72.5	76.7	71.9	87.0	80.8	85.4	81.2	83.5	72.5
Nucleated RBC (/100 WBC)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
HCT (%)	46.3	48.7	49.8	49.2	47.4	51.0	51.7	52.0	53.1	52.2	43.3	43.7	45.8	45.2	46.2	53.8	52.8	48.9	54.9	50.7
Monocyte (/μL)	869	823	1,033	764	1,002	725	485	455	965	950	876	853	939	789	902	603	413	759	743	396
Monocytes (%)	6.3	5.6	4.2	4.6	5.3	5.0	3.7	2.5	5.3	4.5	6.6	6.7	5.42	5.7	6.3	4.1	4.3	4.6	5.9	3.3
Polychromasia	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight

Table 3. Continued 1

Variable	Control group										ABD group									
Time	Preoperation					POD 21					Preoperation					POD 21				
Rat ID	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Anisocytosis	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight
Eosinophil (/μL)	83	29	148	66	132	87	39	36	109	84	83	49	58	76	82	74	38	33	25	24
Eosinophils (%)	0.6	0.2	0.6	0.4	0.7	0.6	0.3	0.2	0.6	0.4	0.5	0.4	0.8	0.3	0.6	0.5	0.4	0.2	0.2	0,2
MCV (fL)	67	67	66	65	75	64	66	67	65	70	58	68	69	55	79	66	66	70	65	67
Basophil (/μL)	14	15	25	33	19	15	13	18	36	21	13	14	20	25	17	29	10	33	13	0
Basophils (%)	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.2	0.1	0.2	0.2	0.1	0.2	0.1	0.2	0.1	0.2	0.1	0.0
MCH (pg)	20.2	20.3	20.1	19.9	22.1	18.6	18.6	19.1	18.6	20.0	20.5	20.2	20.5	20.9	22.9	18.8	19.1	19.9	18.9	19.2
Poikilocytosis	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
Heinz bodies	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
MCHC (g/dL)	30.2	30.2	30.3	30.7	29.5	29.2	28.2	28.7	28.6	28.4	30.3	30.5	30.5	30.7	32.3	28.6	29.0	28.6	29.0	28.8
Metamyelocyte (/μL)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Metamyelocyte (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Myelocyte (/μL)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Platelet count (K/μL)	1,245	1,003	809	845	1,004	861	748	745	667	939	1,365	909	837	898	1,034	614	655	667	720	695
Promyelocyte (/μL)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Promyelocyte (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ALP (U/L)	462	237	351	410	327	326	178	226	214	225	485	337	399	454	437	270	197	211	235	264
AST (U/L)	93	116	131	125	92	57	67	65	57	59	87	96	121	143	99	66	59	64	66	68
ALT (U/L)	51	53	52	48	39	48	57	53	42	32	51	55	42	54	47	45	54	48	45	51
Creatine kinase (U/L)	511	747	893	683	392	76	151	129	125	76	671	768	977	852	535	157	120	93	104	371
Albumin (g/dL)	3.6	3.6	3.6	4.0	3.6	3.8	3.7	3.6	3.8	3.7	3.5	3.6	4.2	4.3	4.1	3.5	3.8	3.5	3.7	3.8
Total bilirubin (mg/dL)	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.2	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.2	0.1
Total protein (g/dL)	6.1	5.8	5.9	6.4	5.8	6.5	6.4	6.6	6.5	6.1	6.8	5.2	5.6	5.4	6.3	6.5	6.6	6.1	6.3	6.4
Globulin (g/dL)	2.5	2.2	2.3	2.4	2.2	2.7	2.7	3.0	2.7	2.4	2.2	2.1	2.4	2.4	2.5	3.0	2.8	2.6	2.6	2.6
Bilirubin, conjugated (mg/dL)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BUN (mg/dL)	13	12	11	13	13	15	18	14	12	15	11	12	13	13	12	11	12	11	13	13
Creatinine (mg/dL)	0.0	0.0	0.1	0.0	0.0	0.3	0.3	0.3	0.3	0.3	0.0	0.0	0.1	0.0	0.0	0.3	0.2	0.2	0.3	0.3
Cholesterol (mg/dL)	115	61	106	112	97	101	65	112	92	92	124	81	94	113	108	111	82	85	64	85
Glucose (mg/dL)	120	134	116	123	121	113	139	107	127	155	116	135	124	133	126	158	132	123	171	136
Calcium (mg/dL)	9.4	9.6	9.6	9.8	9.6	10.6	10.3	10.2	9.8	10.9	9.5	9.7	9.6	9.7	9.7	10.7	11.0	10.5	11.3	12.2
Phosphorus (mg/dL)	9.6	8.7	8.4	9.5	8.6	11.9	8.6	10.1	9.0	10.1	8.4	8.9	8.4	8.5	8.9	10.1	10.6	9.3	10.8	14.3
Bicarbonate TCO_2 (mmol/L)	19	19	20	17	19	26	28	28	27	26	18	19	18	17	18	25	26	32	28	21
Chloride (mmol/L)	Unable to obtain results due to sample dilution					96	95	95	96	94	Unable to obtain results due to sample dilution					97	96	96	98	99

Table 3. Continued 2

Variable	Control group										ABD group									
Time	Preoperation					POD 21					Preoperation					POD 21				
Rat ID	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Potassium (mmol/L)		Unable to obtain results due to sample dilution				8.0	5.9	5.5	5.6	6.1		Unable to obtain results due to sample dilution				6.1	6.4	6.3	7.0	8.4
ALB/GLOB ratio	1.4	1.6	1.6	1.7	1.6	1.4	1.4	1.2	1.4	1.5	1.6	1.7	1.5	1.5	1.7	1.2	1.4	1.3	1.4	1.5
Sodium (mmol/L)		Unable to obtain results due to sample dilution				146	147	146	146	146	Unable to obtain results due to sample dilution					144	146	146	147	146
BUN/creatinine ratio	0	0	0	0	0	50.0	60.0	46.7	40.0	50.0	0	0	0	0	0	36.7	60.0	55.0	43.3	43.3
Bilirubin, unconjugated (mg/dL)	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.2	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.2	0.1
Sodium/potassium ratio		Unable to obtain results due to sample dilution				18	25	27	26	24		Unable to obtain results due to sample dilution				24	23	23	21	17
Hemolysis index			Normal			Normal	+		Normal				Normal			+	Normal	Normal	+	Normal
Lipemia index			Normal					Normal					Normal					Normal		

POD, postoperative day; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; ALB, albumin; GLOB, globulin; TCO_2, total carbon dioxide.

The blood analysis included a complete blood count encompassing 5 different types of WBC: neutrophils, lymphocytes, basophils, eosinophils, and monocytes. A chemistry panel analysis of anticoagulated whole blood and serum was also conducted to evaluate ALP, ALT, total bilirubin, and creatinine levels (Table 3). Blood work was not performed for the Interceed and Seprafilm groups because these well-established interventions are approved and widely used in the clinical context. The weight of all 10 rats that underwent blood analysis was monitored once a week from week 0 (preoperation) until 21 days after the operation.

RESULTS

Swelling and viscoelastic properties

After drying approximately 50 mL of the final mixture in an oven at 50 °C for 24 hours, a uniform film was obtained. The outcome was a flexible film with a thickness of 0.07 ± 0.01 mm (Fig. 3A). The film could be rolled up without breaking and exhibited nonhygroscopic properties (Fig. 3B). The ABD was successfully deployed through trocar ports with diameters ranging from 12 to 14 mm, indicating its suitability for laparoscopic procedures.

Within the 1st hour of the swelling test, Seprafilm and the ABD exhibited substantial swelling of 800% and 1,132%, respectively. Over a 4-day period, the ABD had higher volumetric expansion compared to Seprafilm (Fig. 3C). Notably, the ABD maintained its integrity as a physical film for up to 7 days, after which it became flimsy and gel-like.

The stress-strain relationships were plotted separately for ABD and Seprafilm (Fig. 3D, E). The ABD exhibited a lower elastic modulus than Seprafilm (Table 4), indicating that the ABD can stretch further than Seprafilm under the same applied stress, which is an appealing characteristic for an adhesion barrier.

Phenolic extract

UV-VIS spectroscopy was performed on sporopollenin dissolved in PBS solution at a concentration of 3.7 mg/mL. An average absorbance of 0.0527 at 208 nm was measured, which is about 40 times lower than the absorbance of 2.129 predicted by a linear regression equation for phenolic content in a methanol/water medium (Fig. 4).

Blinded animal study

Surgical trauma was successfully induced in all 40 rats. After the operation, 1 rat in the control group and 2 rats in the ABD group were euthanized due to wound-related complications and self-implicated injury (ripped-out wound clips and chewed open surgical incision). Additionally, 3 rats in the Interceed group and 1 rat in the Seprafilm group died prior to reoperation. Data from

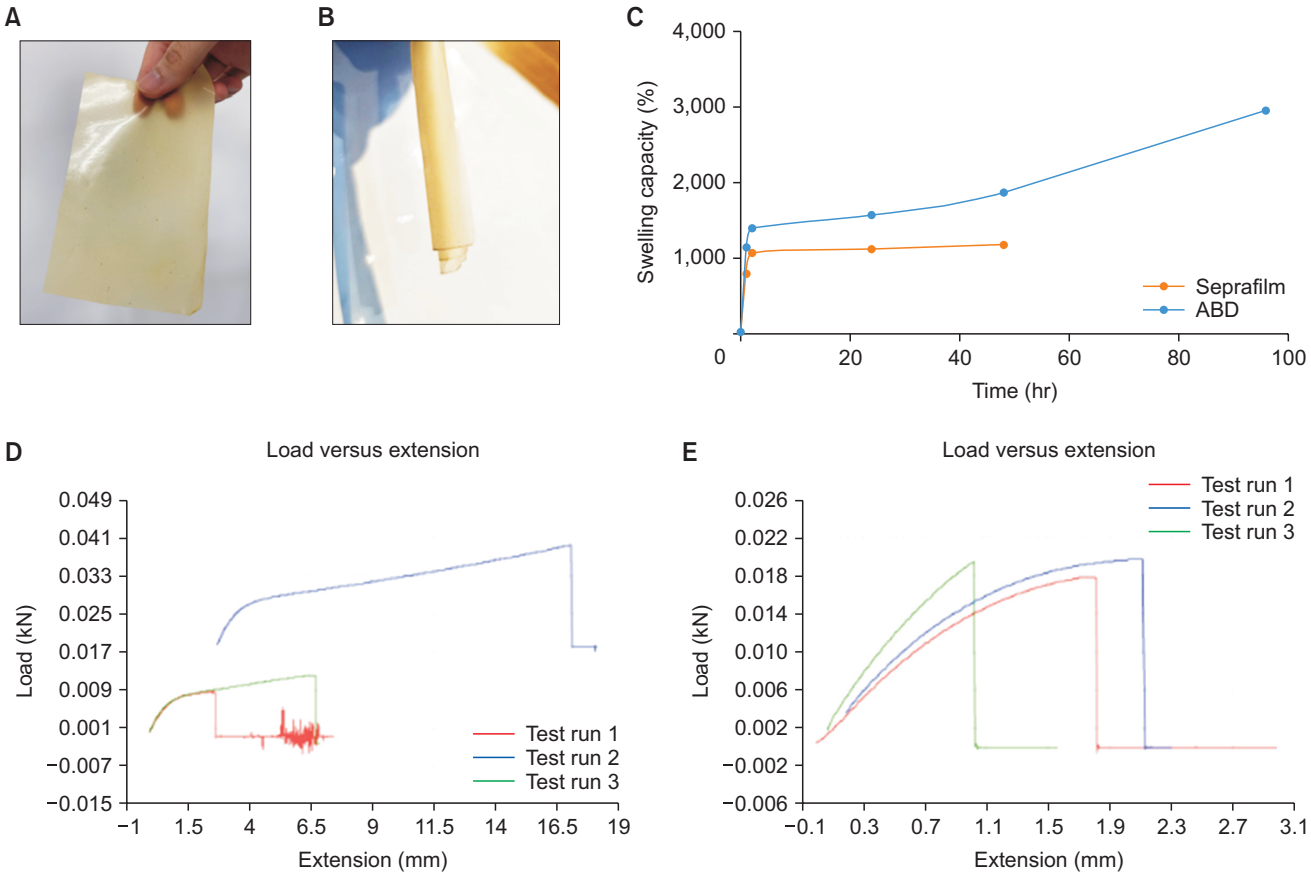

Fig. 3. Physical properties of adhesion barrier device (ABD). (A) ABD of 0.07 mm thickness. (B) Rolled film showcasing the flexibility of the ABD. (C) Comparison of the swelling capacity of Seprafilm (Baxter Healthcare) and ABD over time. (D) Load-extension curves of Seprafilm. (E) Load-extension curves of ABD.

Table 4. Comparison of viscoelastic properties (dry state)

Sample	Thickness (mm)	Run	Peak load/tensile strength (N)	Peak stress (MPa)	Elastic modulus (MPa)
Seprafilm	0.05	Run 1	18.000	24.0	1,147.0
		Run 2	20.000	26.7	1,288.0
		Run 3	19.000	25.3	1,816.0
		Mean ± SD	19.000 ± 1.000	25.3 ± 1.3	1,417.0 ± 353.0
Adhesion barrier device	0.07	Run 1	8.602	8.2	534.191
		Run 2	39.495	37.6	342.849
		Run 3	12.122	11.5	552.767
		Mean ± SD	10.362 ± 2.489	9.9 ± 2.3	543.479 ± 13.135

SD, standard deviation.

all prematurely deceased rats were not included in the analysis. In total, 33 rats (control, 9; Interceed, 7; Seprafilm, 9; and ABD, 8) were evaluated 21 days after surgical-induced trauma.

Upon dissection, no remnants of the barrier materials were observed in the abdominal cavities of any rats in each of the interventional test groups, indicating complete biodegradability of each product, including the ABD.

The mean adhesion severity scores were 3.67 ± 0.50 for the control group, 1.71 ± 1.89 for the Interceed group, 0.89 ± 1.36 for the Seprafilm group, and 0.13 ± 0.35 for the ABD group (Fig. 5). Adhesion severity scores were significantly reduced in the Interceed, Seprafilm, and ABD groups compared to the control group ($P = 0.016$, $P < 0.001$, and $P < 0.001$, respectively), as well as in the ABD group compared to the Interceed group ($P = 0.036$). There was no significant difference in adhesion severity score between the ABD and Seprafilm groups ($P =$

0.070).

Fig. 6 shows the distribution of adhesion severity and area scores for each group. In the control group, 3 rats had adhesion severity scores of 3, and 6 rats had severity scores of 4. In the Interceed and Seprafilm groups, respectively, 3 (42.9%) and 1 (11.1%) rat(s) had scores over 2. None of the rats in the ABD group had adhesion severity scores over 2, and only 1 rat had a grade 1 adhesion. The number of rats with no adhesions was highest in the ABD group (n = 7/8, 7.5%), followed by the Seprafilm group (n = 5/9, 55.6%), and the Interceed group (n = 3/7, 42.9%), respectively. All rats (n = 9) in the control group had adhesions.

The mean adhesion area score was 3.11 ± 1.36 for the control group, 1.29 ± 1.38 for the Interceed group, 0.78 ± 1.30 for the Seprafilm group, and 0.13 ± 0.35 for the ABD group (Fig. 7). The adhesion area scores were significantly lower in the Interceed, Seprafilm, and ABD groups compared to the control group (P = 0.010, P < 0.001, and P < 0.001, respectively), as well as in the ABD group compared to the Interceed group (P = 0.034). There was no significant difference in the adhesion area scores of the ABD and Seprafilm groups.

The adhesion severity score was correlated with the adhesion

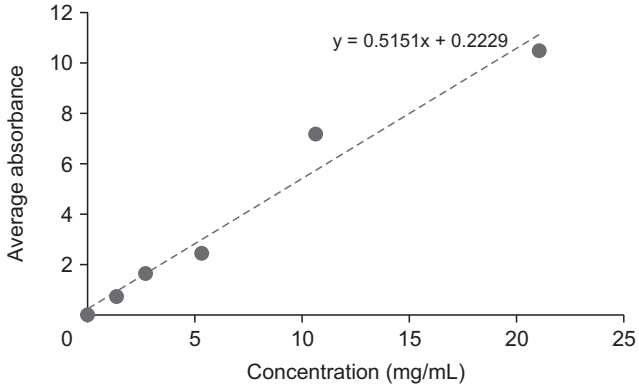

Fig. 4. Ultraviolet-visible absorption spectra of cleaned sporopollenin at different concentrations. The phenolic content concentration of cleaned sporopollenin obtained through linear regression analysis.

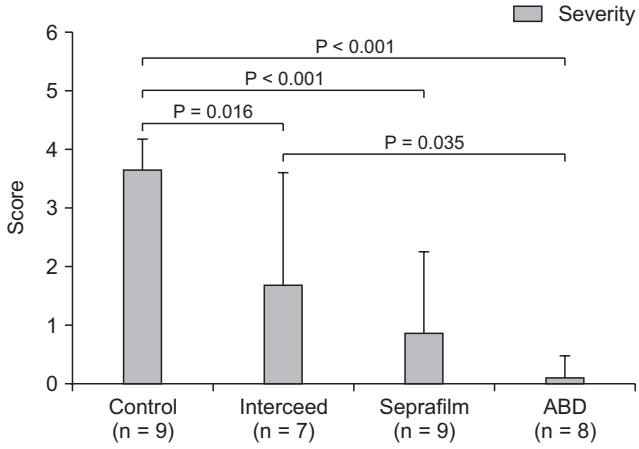

Fig. 5. Comparison of adhesion severity scores (mean ± standard deviation) 21 days after injury. Adhesion severity scores were analyzed using 1-tailed t-tests. All study groups had significantly lower adhesion severity compared to the control group (P < 0.05 to P < 0.001). The adhesion barrier device (ABD) group showed significantly (P = 0.035) lower adhesion severity compared to the Interceed group. No significant difference in adhesion severity scores was found between the ABD and Seprafilm groups (P = 0.070). P-values <0.05 were considered statistically significant. Interceed: Gynecare, Ethicon, Johnson & Johnson Company; Seprafilm: Baxter Healthcare.

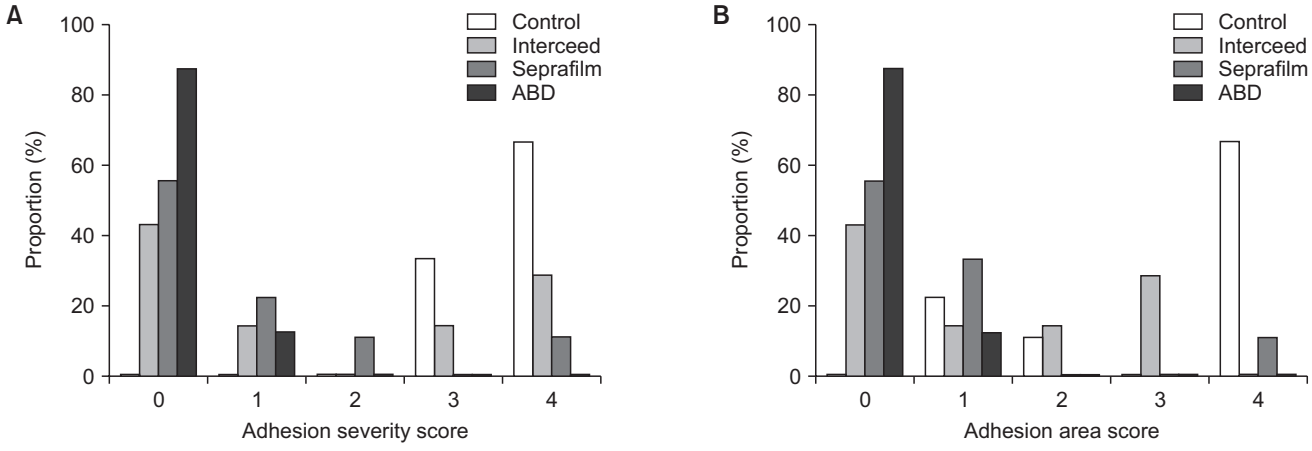

Fig. 6. Distribution of adhesion severity and area score by study group. The severity and area of adhesion between the cecum and abdominal wall were evaluated by a blinded researcher according to the Adhesion Severity and Adhesion Area Scoring Scheme, with a score of 0 representing no adhesions and a score of 4 representing adhesion to 75%–100% of the initial injured area. The adhesion barrier device (ABD) performed the best, with the highest number of rats with no adhesion (n = 7/8, 87.5%), followed by the Seprafilm group (n = 5/9, 55.6%) and the Interceed group (n = 3/7, 42.9%), respectively. All rats (n = 9) in the control group had adhesions. (A) Distribution of adhesion severity score. (B) Distribution of adhesion area score.

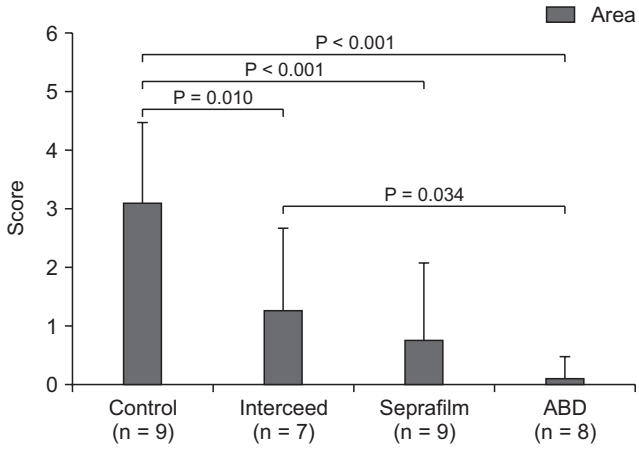

Fig. 7. Comparison of adhesion area scores (mean ± standard deviation) 21 days after injury. Adhesion area scores were analyzed using 1-tailed t-tests. All groups had significantly lower adhesion area compared to the control group ($P < 0.05$ to $P < 0.001$). The adhesion barrier device (ABD) group showed significantly ($P = 0.034$) lower adhesion area compared to the Interceed group. No significant difference in adhesion area score was found between the ABD and Seprafilm group ($P = 0.091$). P-values <0.05 were considered statistically significant. Interceed: Gynecare, Ethicon, Johnson & Johnson Company; Seprafilm: Baxter Healthcare.

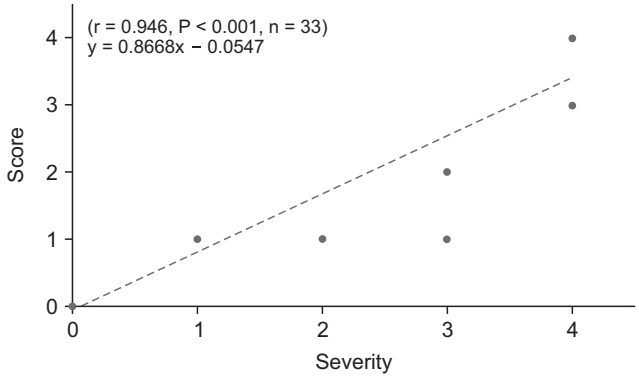

Fig. 8. Comparison of adhesion severity and adhesion area score. Each animal (n = 33) is represented by a single point. A strong correlation was shown between the 2 adhesion measures.

area score with a significant linear correlation ($r = 0.946$, $P < 0.001$, $n = 33$) (Fig. 8).

Blood chemistry

The blood analysis on day 21 after the operation showed significant differences in mean overall WBC count and mean lymphocyte count between the control and ABD groups (Fig. 9). The mean overall WBC count was 17,020 ± 3,207/μL for the control group, and 13,080 ± 2,638/μL for the ABD group ($P = 0.033$). The mean lymphocyte count was 13,886 ± 2,472/μL for the control group and 10,539 ± 2,169/μL for the ABD ($P = 0.026$).

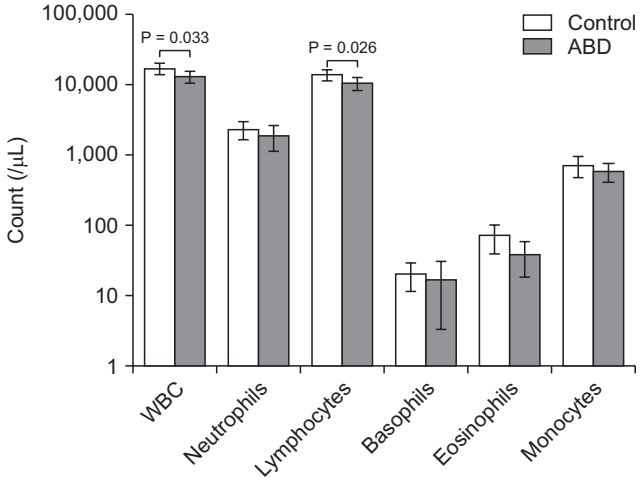

Fig. 9. Comparison of WBC in anticoagulated whole blood between rats in the control and adhesion barrier device (ABD) group 21 days after surgery. Cell counts were analyzed using 1-tailed t-tests. There was a significant decrease in the overall WBC ($P = 0.033$) and lymphocyte count ($P = 0.026$) for the ABD group compared to the control group, with no significant difference for the neutrophils ($P = 0.191$), basophils ($P = 0.320$), eosinophils ($P = 0.050$), and monocytes count ($P = 0.177$) between the control and ABD group. P-values <0.05 were considered statistically significant.

The mean neutrophil, basophil, eosinophil, and monocyte counts were not significantly different between groups, but the control group consistently demonstrated higher inflammatory marker counts compared to the ABD group (Fig. 9). The mean neutrophil count was 2,326 ± 663/μL for the control group and 1,902 ± 780/μL for the ABD group. The mean basophil count was 21 ± 9/μL for the control group and 17 ± 14/μL for the ABD group. The mean eosinophil count was 71 ± 32/μL for the control group and 39 ± 21/μL for the ABD group. The mean monocyte count was 716 ± 244/μL for the control group and 583 ± 174/μL for the ABD group. There was a significant decrease in the overall WBC ($P = 0.033$) and lymphocyte count ($P = 0.026$) for the ABD group compared to the control group.

The serum chemistry panel on day 21 after the operation showed that the ALP, ALT, total bilirubin, and creatinine levels were all within normal range and with no significant difference between the control and ABD groups (Fig. 10). The size of each rat was also comparable to each other with no significant difference in weight.

Histological analysis

Histological analysis was performed on the rats from the ABD group. As shown in Fig. 11, in the section of skin and abdominal wall, the deep surface that lines the abdominal wall contains a moderately dense infiltrate of macrophages with lacy basophilic cytoplasm, lymphocytes, and scattered multinucleated cells containing lightly basophilic cytoplasmic material. There is a

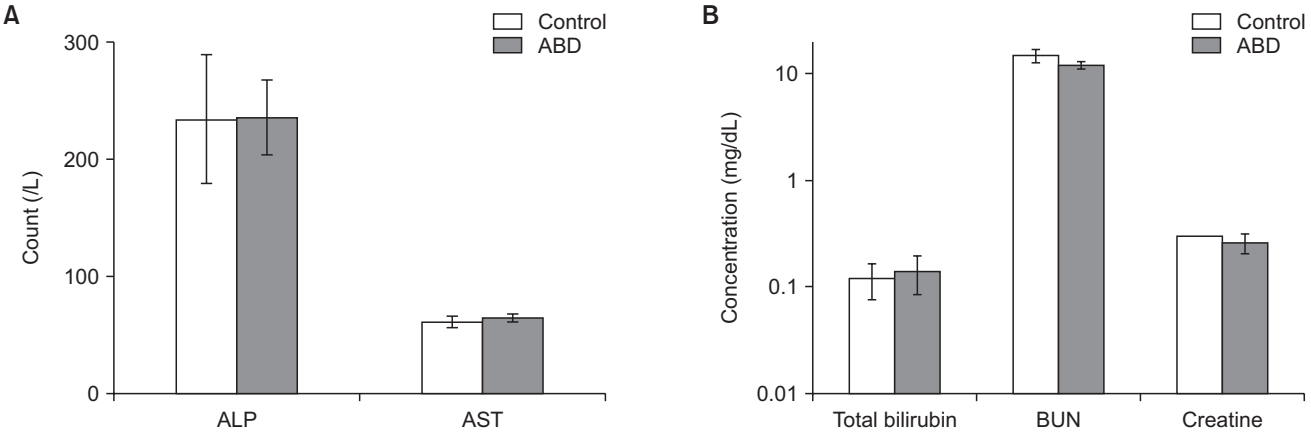

Fig. 10. Comparison of blood chemistry markers in serum extracted from rats in the control and adhesion barrier device (ABD) groups 21 days after surgery. No significant difference in the blood chemistry markers between the control group and the ABD group was found. (A) ALP, ALT. (B) Total bilirubin, BUN, and creatinine.

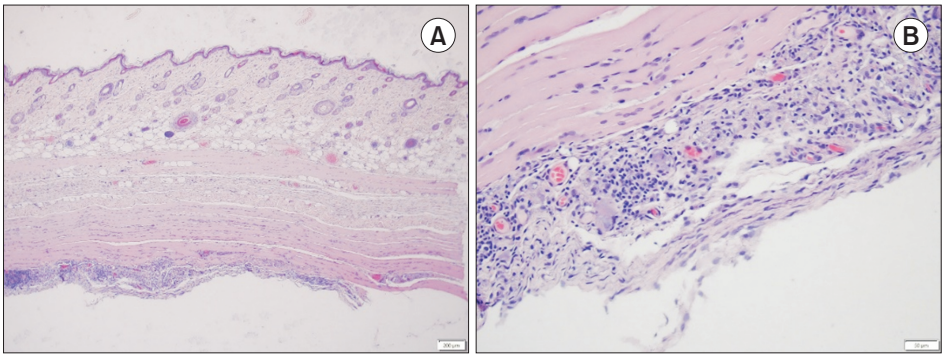

Fig. 11. Histological analysis of tissue. Representative H&E-stained pathological images of rats from the adhesion barrier device group under 4× (A) and 20× (B) magnification using optical microscopy.

focal area of mild acanthosis and dermal fibrosis at one end of the section of skin. Overall, there are no drastic fibrotic and inflammatory change on the tissue.

DISCUSSION

We conducted a 4-arm, controlled, blinded, experimental study to assess the efficacy of a sporopollenin-based ABD in preventing postsurgical abdominal adhesions using a murine model.

Rats were assigned to Interceed, Seprafilm, ABD, or control groups, and surgical trauma was induced, followed by the application of respective adhesion barriers in the intervention groups. At 21 days after the operation, surgical adhesion severity and area scores were significantly reduced in all 3 intervention groups compared to the control group, and in the ABD group compared to the Interceed group. Blood chemistry showed higher levels of inflammatory markers in the control group compared to the ABD group.

Upon dissection, no remnants of the ABD were observed in the abdominal cavities of any rats in the ABD group, indicating complete biodegradation of the product. This is supported by previous literature investigating the different constituents of the ABD [14-21]. In an *ex vivo* study, sporopollenin was shown to partially degrade in human blood plasma, resulting in bulk erosion into 40 μm-sized fragments that are too large to be absorbed into the systemic circulation [14].

Recent research has focused on preventing intra-abdominal adhesions. Despite recent advancements in our understanding of the pathogenesis of adhesion formation [5], identifying the optimal substance to prevent their occurrence remains challenging. Challenges associated with applying solid barriers during surgical procedures have led to the development of sprayable polymer solutions which typically include chitosan, hyaluronic acid, CMC, and/or nanoparticles-supramolecular polymeric hydrogel [1-3,8,9]. While sprayable polymer solutions are simple to apply, they are often only moderately effective in preventing adhesions due to their short residence time or inflamed tissue at the site of injury [10,11]. Consequently, barrier films continue to be applied as standard practice for preventing adhesions in various surgical procedures [13,14,16,17,22-25].

In our animal study, Interceed is not as effective as Seprafilm and ABD in the prevention of adhesion most likely due to the presence of bleeding. It has been reported in another

animal study [6] that a modified form of Interceed, nTC7, has a neutral surface pH of 5. As compared to the original Interceed which has a lower pH of 2, nTC7 showed better efficacy due to the swollen fabric of the gauze material upon contact with denatured proteins from serum or lysed erythrocytes leading to pore closure of the gauze and a complete adhesion barrier for improved coverage. As shown in Fig. 2, both Seprafilm and ABD are in the form of a complete film overcoming the limitation of the open pore structure of the gauze form presented in Interceed.

When developing the ABD, we intentionally omitted sodium hyaluronate from the ABD's composition to increase its flexibility for optimal use during laparoscopic procedures. The mechanical properties of the ABD were enhanced by incorporating polyanionic sporopollenin with polycationic dextran into the formulation and reinforcing the microscopic opposite charge attachment through crosslinking with CA. This strategy enhanced the mechanical integrity of the hydrocolloid film in a physiological medium by at least 7 days (Fig. 3D). This is important since the normal healing process takes around 1 week and involves the regeneration of the damaged mesothelial layer to heal both small and large peritoneal defects [20]. In this regard, the ABD has a clear advantage over Seprafilm which hydrates to form a lubricious gel coating within 24 to 48 hours of placement [23]. Moreover, in the dry state, the ABD appears to offer improved usability over Seprafilm because it has a lower elastic modulus, as shown in Table 4. In comparison to the stiff nature of Seprafilm, the rubber-like nature of the ABD translates to less tearing and cracking of the film, both before and during deployment. Especially for minimally invasive surgery, the ABD rolls sufficiently to enable it to fit through the keyhole (Fig. 3C), unlike Seprafilm which is very challenging to roll up without cracking.

The serum chemistry panel on day 21 after the operation showed normal ALP, ALT, total bilirubin, and creatinine levels in both the control and ABD groups, indicating there was no kidney or liver injury caused by the metabolism of ABD (Table 3). In previous pharmacokinetics studies, CMC was shown to have been absorbed as macromolecules into the capillaries of the peritoneal cavity of rats and transported to the liver, spleen, and pancreas to be broken down [22]. A previous pharmacokinetics study performed on animal and human using Seprafilm, which contains CMC, showed that CMC was resorbed at the site of application within 7 days, and was totally cleared from the system by 28 days [23]. Furthermore, PEG detected in blood samples of mice that had been injected with PEG2000 solution was shown to be cleared within 8 hours of administration. Human studies have demonstrated that PEG is excreted via the kidneys within 12 hours of administration [16,24]. Similarly, dextran has been demonstrated to be excreted unchanged in human urine, if its molecular weight does not exceed 50 kilodalton (kDa). At higher molecular weights, it is not renally eliminated in any significant amount [17]. Of note, the ABD investigated in the current study contains dextran-40, which has a molecular weight of 40 kDa, which is below the weight threshold for unrestricted glomerular filtration. CA (vitamin C) has been shown to be absorbed into the systemic circulation of rats and has significant protective effects against oxidative damage in the blood, liver, and muscle [20].

Phenolic compounds such as flavonoids, phenolic acids, fatty acids, and phytosterols found in the exine of sunflower (*Helianthus annuus* L.) pollen have been documented to induce an anti-inflammatory response [12,26]. During the development of the ABD, allergenic components of pollen in the internal compartment of pollen exine shells were removed by alkaline hydrolysis [12,26], leaving sporopollenin behind. The ABD was subjected to stringent biocompatibility standard testing (ISO 10993) and was shown to adhere to all relevant requirements after implantation of biomaterials including negligible levels of cytotoxicity, systemic toxicity, genotoxicity, irritation, sensitization, and local effects.

Given that in our animal models, the implanted sporopollenin in ABD was in contact with a physiological medium rather than a methanol/water medium, based on the UV-VIS spectroscopy results (Fig. 4), we hypothesize that a small amount of phenolic leaching may have contributed to the slightly lower WBC count in the ABD group as compared to the control group. The modulation of inflammation response may have contributed as an adjunct to the prevention of adhesions in our animal model using ABD.

There are several limitations in this study. First, the study utilized a small number of rats and the follow-up period was short. As a result, we were unable to comprehensively assess the potential long-term effects of the ABD. Nonetheless, within the constraints of our study's scale and duration, we successfully demonstrated the superior antiadhesive properties of the ABD compared to both the control group and Interceed. This finding is important and suggests that the ABD exhibits promising antiadhesive effects. Second, the research was conducted exclusively in the colons of rats. Extrapolation of our findings to humans is therefore constrained and necessitates caution. We acknowledge that there is a need for further research to bridge the gap between experimental models and clinical application to enhance the relevance and utility of our findings in clinical practice. Future studies are warranted to evaluate the antiadhesive effects of the ABD in humans.

We demonstrated the antiadhesive effect of a sporopollenin-based ABD using a randomized, blinded, controlled animal study. The ABD was shown to be safe and have better antiadhesive effects than both no intervention and Interceed, and comparable efficacy to Seprafilm. The ABD may be a valuable option in overcoming limitations observed in Seprafilm

and Interceed such as material brittleness and compatibility with surgeries involving blood fields. While the ABD was shown to reduce the risk of adhesions in abdominal surgeries in rats, further investigation about its safety and efficacy in humans through pivotal clinical trials involving different anatomical sites is required prior to commercialization.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Fatehi Hassanabad A, Zarzycki AN, Jeon K, Deniset JF, Fedak PW. Post-operative adhesions: a comprehensive review of mechanisms. Biomedicines 2021;9:867.
2. Sirovy M, Krupova M, Hyspler R, Ticha A, Kolackova M, Andrys C, et al. Lipid emulsions prevent postoperative abdominal adhesions. Asian J Surg 2023;46:465-71.
3. Stapleton LM, Steele AN, Wang H, Lopez Hernandez H, Yu AC, Paulsen MJ, et al. Use of a supramolecular polymeric hydrogel as an effective post-operative pericardial adhesion barrier. Nat Biomed Eng 2019;3:611-20.
4. Yu HW, Lee D, Lee K, Kim SJ, Chai YJ, Kim HC, et al. Effect of an anti-adhesion agent on vision-based assessment of cervical adhesions after thyroid surgery: randomized, placebo-controlled trial. Sci Rep 2021;11:19935.
5. Ghobrial S, Ott J, Parry JP. An overview of postoperative intraabdominal adhesions and their role on female infertility: a narrative review. J Clin Med 2023;12:2263.
6. Wiseman DM, Gottlick-Iarkowski L, Kamp L. Effect of different barriers of oxidized regenerated cellulose (ORC) on cecal and sidewall adhesions in the presence and absence of bleeding. J Invest Surg 1999;12:141-6.
7. Ahmad G, O'Flynn H, Hindocha A, Watson A. Barrier agents for adhesion prevention after gynaecological surgery. Cochrane Database Syst Rev 2015;2015:CD000475.
8. Ahn JH, Yoon SG, Yi JW, Kim SJ, Lee KE. Anti-adhesive effect and safety of a thermosensitive adhesion barrier (Mediclore) for thyroid surgery: a double-blinded randomized controlled trial. Ann Surg Treat Res 2022;102:313-22.
9. Ourani-Pourdashti S, Azadi A. Pollens in therapeutic/diagnostic systems and immune system targeting. J Control Release 2021;340:308-17.
10. Diego-Taboada A, Beckett ST, Atkin SL, Mackenzie G. Hollow pollen shells to enhance drug delivery. Pharmaceutics 2014;6:80-96.
11. Rzepecka-Stojko A, Stojko J, Kurek-Górecka A, Górecki M, Kabała-Dzik A, Kubina R, et al. Polyphenols from bee pollen: structure, absorption, metabolism and biological activity. Molecules 2015;20:21732-49.
12. Kostić AŽ, Milinčić DD, Gašić UM, Nedić N, Stanojević SP, Tešić ŽL, et al. Polyphenolic profile and antioxidant properties of bee-collected pollen from sunflower (Helianthus annuus L.) plant. LWT 2019;112:108244.
13. Vlahos A, Yu P, Lucas CE, Ledgerwood AM. Effect of a composite membrane of chitosan and poloxamer gel on postoperative adhesive interactions. Am Surg 2001;67:15-21.
14. Fan TF, Potroz MG, Tan EL, Park JH, Miyako E, Cho NJ. Human blood plasma catalyses the degradation of Lycopodium plant sporoderm microcapsules. Sci Rep 2019;9:2944.
15. Artzi N, Oliva N, Puron C, Shitreet S, Artzi S, bon Ramos A, et al. In vivo and in vitro tracking of erosion in biodegradable materials using non-invasive fluorescence imaging. Nat Mater 2011;10:704-9.
16. Mattheolabakis G, Wong CC, Sun Y, Amella CA, Richards R, Constantinides PP, et al.

Pegylation improves the pharmacokinetics and bioavailability of small-molecule drugs hydrolyzable by esterases: a study of phospho-Ibuprofen. J Pharmacol Exp Ther 2014;351:61-6.
17. Drugbank. Dextran [Internet]. Drugbank; 2024 [cited 2024 Apr 23]. Available from: https://go.drugbank.com/drugs/DB09255
18. Pellegrini G, Starkey Lewis PJ, Palmer L, Hetzel U, Goldring CE, Park BK, et al. Intraperitoneal administration of high doses of polyethylene glycol (PEG) causes hepatic subcapsular necrosis and low-grade peritonitis with a rise in hepatic biomarkers. Toxicology 2013;314:262-6.
19. Fan C, Hou L, Che G, Shi Y, Liu X, Sun L, et al. Dose- and time-dependent systemic adverse reactions of sodium carboxy methyl cellulose after intraperitoneal application in rats. J Toxicol Sci 2021;46: 223-34.
20. Cay M, Naziroğlu M, Simsek H, Aydilek N, Aksakal M, Demirci M. Effects of intraperitoneally administered vitamin C on antioxidative defense mechanism in rats with diabetes induced by streptozotocin. Res Exp Med (Berl) 2001;200:205-13.
21. Jones CI, Payne DA, Hayes PD, Naylor AR, Bell PR, Thompson MM, et al. The antithrombotic effect of dextran-40 in man is due to enhanced fibrinolysis in vivo. J Vasc Surg 2008;48:715-22.
22. Hirszel P, Shea-Donohue T, Chakrabarti E, Montcalm E, Maher JF. The role of the capillary wall in restricting diffusion of macromolecules: a study of peritoneal clearance of dextrans. Nephron 1988;49: 58-61.
23. Diamond MP, Burns EL, Accomando B, Mian S, Holmdahl L. Seprafilm® adhesion barrier: (1) a review of preclinical, animal, and human investigational studies. Gynecol Surg 2012;9:237-45.
24. Drugbank. Polyethylene glycol [Internet]. Drugbank; 2024 [cited 2024 Apr 23]. Available from: https://go.drugbank.com/drugs/DB09287
25. Kim JY, Cho WJ, Kim JH, Lim SH, Kim HJ, Lee YW, et al. Efficacy and safety of hyaluronate membrane in the rabbit cecum-abdominal wall adhesion model. J Korean Surg Soc 2013;85:51-7.
26. Kilani-Jaziri S, Mokdad-Bzeouich I, Krifa M, Nasr N, Ghedira K, Chekir-Ghedira L. Immunomodulatory and cellular anti-oxidant activities of caffeic, ferulic, and p-coumaric phenolic acids: a structure-activity relationship study. Drug Chem Toxicol 2017;40:416-24.