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RESEARCH ARTICLE

A Comparison of the Efficacy of Dimethyl Sulfoxide (DMSO) and Synovial Fluid in the Prevention of Peritoneal Adhesions: Experimental Rabbit Model [1]

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Summary

The purpose of this study was to compare the efficacy of dimethyl sulfoxide and synovial fluid (SF) in the prevention of peritoneal adhesions that might develop in connection with the use of mersilen mesh in a ventral hernia model created experimentally in rabbits. The forty rabbits used in the study were divided into four groups of ten. The operation was conducted under intrathecal anesthesia induced with ketamine HCl (20 mg/kg intrathecal) following xylazin HCl (5 mg/kg intramuscular) sedation. A median skin incision was made in rabbits placed on the operating table in the supine position. Then, a defect 2 cm in diameter was created on the linea alba. The defect was repaired with mersilen mesh which had been previously prepared in the shape of a disk. Until the 7th day after the operation, group I was given 10 ml saline (S) and 1.5 g/kg DMSO, group II was given 7 ml saline, 3 ml synovial fluid (SF) and 1.5 g/kg DMSO, group III was given 7 ml saline and 3 ml SF while group IV (control: C) was given only 10 ml saline. All of these were administered intraperitoneally. At the end of the 10th day, the presence and extent of peritoneal adhesion was checked using Jenkins' (1983) visual adhesion scale by performing a relaparotomy. All of the data obtained from the study was analyzed statistically using the Minitab-16 package program. Tissue samples from the region where the graft was performed were evaluated under a light microscope by staining them with the Hematoxilen-Eosin (HE) and Crossman triple stain method. The results of the adhesion scale were evaluated nonparametrically and statistical calculations were performed with the Kruskal-Wallis test. No statistical difference was found between the groups (P>0.05). The results of histopathological examination revealed that the tissue which covered the graft in all of the groups was fibrous tissue. However, it was determined that the fibrosis was weaker in the DMSO group than it was in the SF-DMSO, SF and S groups. In the end, it was concluded that synovial fluid is effective in preventing postoperative peritoneal adhesions in rabbits in light of both relaparotomic, macroscopic findings and histopathological findings.

Keywords: *Rabbit, Intraabdominal adhesion, Dimethylsulfoxide, Synovial fluid*

Peritoneal Adezyonların Önlenmesinde Dimetil Sülfoksit (DMSO) ve Synovial Sıvı Etkinliğinin Karşılaştırılması: Deneysel Tavşan Modeli

Özet

Bu çalışmada, tavşanlarda deneysel olarak oluşturulan ventral herni modelinde mersilen mesh kullanımına bağlı gelişebilecek peritoneal adezyonların önlenmesinde dimetil sülfoksit ve sinovial sıvı etkinliğinin karşılaştırılması amaçlandı. Çalışmada kullanılan 40 tavşan 4 gruba ayrıldı (n: 10). Operasyon xylazin HCl (5mg/kg im) sedasyonunu izleyerek ketamin HCl (20 mg/kg intratekal) ile elde edilen intratekal anestezi altında gerçekleştirildi. Operasyon masasına sırtüstü pozisyonda yatırılan tavşanlara median deri insizyonu yapıldıktan sonra linea alba düzeyinde 2 cm çaplı daire şeklinde bir defekt oluşturuldu. Defekt önceden disk şeklinde hazırlanan mersilen mesh ile onarıldı. Postoperatif 7. güne kadar; I. gruba 10 ml serum fizyolojik (SF) ve 1.5 g/kg DMSO, II. gruba 7 ml SF, 3 ml synovial sıvı (SS) ve 1.5 g/kg DMSO, III. Gruba 7 ml SF ve 3 ml SS, IV. gruba (kontrol: K) ise yalnızca 10 ml SF intraperitoneal olarak uygulandı. Tavşanlara 10. günün sonunda relaparotomi uygulanarak peritoneal adezyon varlığı ve derecesi Jenkins (1983)'in görsel yapışıklık skalasına göre değerlendirildi. Çalışmadan elde edilen tüm veriler Minitab-16 paket programı kullanılarak istatistiksel olarak değerlendirildi. Greft uygulanan bölgeye ait doku örnekleri Hematoksilen-Eozin (HE) ve Crossman'ın üçlü boyama yöntemi ile boyanarak ışık mikroskobunda değerlendirildi. Nonparametrik olarak değerlendirilen yapışıklık skala sonuçları Kruskal-Wallis testi ile istatistiki olarak hesaplandı ve gruplar arasında anlamlı bir fark bulunmadı (P>0.05). Histopatalojik inceleme sonuçları ise tüm gruplarda greftin üzerini örten dokunun fibröz doku karakterinde olduğunu gösterdi. Bununla birlikte fibrozisin DMSO grubunda, ES-DMSO, ES ve SF grubuna göre daha zayıf olduğu tespit edildi. Sonuçta gerek relaparotomik makroskobik bulgular gerekse histopatolojik bulgular dikkate alındığında synovial sıvının tavşanlarda postoperatif peritoneal adezyonların önlenmesinde etkili olduğu sonucuna varıldı.

Anahtar sözcükler: *Tavşan, İntraabdominal adezyon, Dimetilsülfoksit, Synovial sıvı*

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INTRODUCTION

Ventral hernias occur due to a variety of reasons either as a primary condition or as a result of complications arising during surgical procedures (incisional hernia) [1-5]. In situations where there is insufficient healthy tissue or when the hernia rupture is very large, prosthetic materials are used in treatment. These materials are applied as a patch either above or below the fascia. If the mesh comes into contact with abdominal organs, serious intraabdominal adhesions form [1-11].

The surface of the peritoneum is covered by mesothelium cells arranged in a single layer [7,8,12]. Regardless of the size of the defect created as a result of trauma, it is repaired by the mesothelium cells in the surrounding area within 3-5 days [13]. The rapid healing potential of the peritoneum and its unique physiological characteristics plays an important role both in the formation of intraabdominal adhesions and their prevention [5,7-13].

Peritoneal adhesions generally occur as fibrous bands that develop between the serosal surfaces of nearby organs, and the most important causes are previous operations, foreign objects and ischemia [1-8,11]. Trauma suppresses fibrinolytic activity and stimulates the secretion of histamine and vasoactive kinins, thereby increasing capillary permeability. As a result, a seroangiotic fluid is created which plays a role in the formation of fibrous bands between the peritoneal cavity and nearby organs [12]. Adhesions which develop due to the use of polypropylene mesh can be explained as a foreign body reaction that develops due to the mesh and as a decline in plasminogen activation due to the effect on the parietal layer [7-13]. Fibrinolytics, anticoagulants, anti-inflammatory agents, antibiotics and a number of materials that create a physical barrier are being studied for their effectiveness in preventing these adhesions which can cause intestinal obstructions, volvulus, infertility and abdominal pain [1,3-5,7,8,11,12,14-20].

Dimethyl sulfoxide (DMSO) is used for a variety of purposes in industry. It is also commonly used in medicine due to its anti-inflammatory, anti-coagulant, diuretic, analgesic and fibroblast proliferation inhibiting characteristics [7,8,21,22].

Hyaluronic acid is a polyelectrolyte with a long, linear negative electrical load. It is used in various formulations in a number of clinical fields, primarily orthopedics, ophthalmology and dermatology [23]. Due to its high viscosity, anti-inflammatory, antioxidant, and anti proliferative effects, it has found an application in surgical clinics in recent years for the purpose of preventing adhesions. One of the places in the body with the highest concentrations of HA, which is also a glycosaminoglycan, is synovial fluid [20,23-26]. HA gives synovial fluid its viscosity and its concentration in bovine synovial fluid is 2-4 mg mL [20,26].

The purpose of this study was to compare the efficacy of DMSO and bovine synovial fluid, which was used as a source of HA, in preventing the intraabdominal adhesions that might occur in connection with the mersilene mesh which is preferred for repair in experimental ventral hernia models in rabbits.

MATERIAL and METHODS

The Ethic Committee on Research Animal Care at Kafkas University of Kars, Turkey approved all procedures in this study (No: KAÜ-HADYEK-2012/52).

Animal Material

Forty adult New Zealand rabbits of the same age and gender with an average live weight of 2.5-4 kg were divided into four groups of ten. The rabbits were fed ad libitum with standard rabbit food prior to and following the surgery.

Acquisition of Synovial Fluid

Sinovial fluid obtained under sterile conditions from the tarsal joints of cattle which had undergone a multifaceted health screening was subjected to a physical examination focusing on color, appearance and viscosity. After determining the quality and quantity of the hyaluronic acid contained in the collected sinovial fluid with the Mucin-clot test, it was centrifuged to obtain the supernatant used in the study.

Stages of Implementation

Xylazin HCl (5 mg/kg IM) (Rompun-Bayer 2%) sedation and intrathechal anesthesia achieved with ketamine HCl (20 mg/kg) (Ketalar-Parkedavis) were chosen for the operation. The rabbits were laid supine on the operating table, and their abdominal areas were shaved and disinfected, after which the area was opened with a median incision approximately 4 cm long. A defect measuring 2 cm in

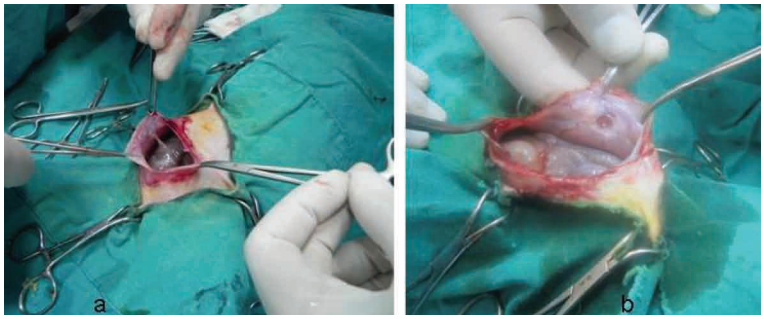

Fig 1. Macroscopic view during relaparotomy (a- Occurrence of adhesion, b- Graft completely covered with peritoneum without adhesion)

Şekil 1. Relaparatomik makroskobik görüntü (a- Adezyon oluşumu, b- Greftin adezyon olmaksızın peritonla tamamen örtülmüş hali)

diameter and including the linea alba was created to open the abdominal cavity. The defect that was created was closed up with polypropylene mesh in the shape of a disc *(Fig. 1)* as an inlay while the skin and subcutaneous connective tissue were closed routinely. 3/0 polyglactin 910 (Vicryl-Ethicon) was chosen to secure the mesh to the abdominal wall. The following treatments were administered intraperitoneally to each group in accordance with the following protocols once a day from the first day of the operation to the seventh day:

Group I: 10 ml saline and 1.5 g/kg DMSO

Group II: 7 ml saline, 3 ml SF and 1.5 g/kg DMSO

Group III: 7 ml saline and 3 ml SF

Group IV: Only 10 ml of saline (control: C)

The body temperatures, respiratory rates and pulse of the rabbits were recorded at regular intervals before, during and after the procedure. Parenteral analgesia (75 mg/kg, IM, Metamizol Sodium, Bulb, Novalgin®, Sanofi, Turkey) and antibiotics (5 mg/kg, IM, Enroflaksasin, Via, Baytril® 2.5%, Bayer, Turkey) were administered for three days following surgery.

Ten days later, the abdominal cavity was opened with a paramedian relaparotomy following the same anesthetic protocol. The existence of an intraabdominal adhesion and its extent was evaluated according to the visual adhesion scale of Jenkins et al.[13]. After taking the tissue samples required for histopathological evaluation, the laparotomy incision of the rabbits was closed with recognized methods and care was taken to ensure their survival with postoperative care and feeding.

Histopathological Examination

A circular piece was removed from the area where the graft was performed including some of the surrounding tissue and it was preserved in a 10% formaldehyde solution for histopathological examination. The tissues were blocked in paraffin after routine laboratory procedures. Cross-sections five microns thick were taken from the blocks that had been prepared and subjected to light microscopic evaluation by staining with Hematoxilen-Eosin (HE) and Crossman's triple staining technique. The cross-sections which were stained with Crossman's triple staining technique were examined for the formation and organization of fibrous tissue. The cross-sections stained with HE were evaluated for leukocyte infiltration, foreign-body giant cells, fibrosis, capillarization and necrosis.

Statistics

The Minitab-16 package program was used on all of the data obtained in the study. First of all, the data were subjected to the normality test. Then, statistical evaluation was conducted between the groups using the ANOVA method (One-way Analysis of Variance Tukey's pairwise comparisons) for parametric values while the Kruskal Wallis test was used on non-parametric values. $P<0.05$ was considered significant.

RESULTS

Pulse and respiratory rates and body temperatures were measured and recorded for all of the animals in the first three days after the operation *(Table 1)*. No statistically significant difference was found between the groups for any of these values ($P>0.05$).

The area to which the graft was applied prior to relaparotomy was evaluated with palpation and no abnormalities were found. The abdominal cavity was accessed via an approximately 5 cm incision 1-2 cm lateral from the graft, and then the peritoneal surface of the region facing the abdomen and to which the graft had been applied was examined. A single stage-1 adhesion (fibrin band) approximately 0.4 cm wide and 4 cm long was identified between the center of the graft and an organ in 2 subjects from groups I and IV and 1 subject from group II *(Fig. 2)*. In all of the cases, the graft was covered with a shiny layer consistent with peritoneum *(Fig, 3)*.

Table 1. *Statistical distribution of postoperative pulse, respiration and body temperatures*
Tablo 1. *Postoperatif nabız, solunum ve vücut ısılarının istatistiksel dağılımı*

Values		Group I	Group II	Group III	Group IV
Pulse	Day 1	146.30±12.74 [a]	161.50±5.17 [a]	168.10±25.99 [a]	157.10±18.49 [a]
	Day 2	135.00±35.91 [a]	144.40±8.49 [a]	157.80±37.69 [a]	147.20±37.43 [a]
	Day 3	153.60±23.75 [a]	146.00±19.32 [a]	149.60±36.72 [a]	149.00±31.33 [a]
Respiration	Day 1	56.90±5.78 [a]	77.40±28.03 [a]	58.00±7.06 [a]	64.50±23.52 [a]
	Day 2	64.10±15.74 [a]	55.90±10.14 [a]	70.80±19.21 [a]	55.70±9.87 [a]
	Day 3	70.40±7.53 [a]	78.70±13.90 [a]	84.80±4.13 [a]	75.40±14.82 [a]
Temperature	Day 1	37.53±0.27 [a]	37.49±9.31 [a]	38.42±0.60 [a]	37.50±0.45 [a]
	Day 2	37.79±0.71 [a]	37.75±0.45 [a]	38.14±0.61 [a]	37.83±0.57 [a]
	Day 3	37.69±0.39 [a]	37.86±0.59 [a]	37.74±0.53 [a]	37.79±0.57 [a]

a- *There was no difference between the mean values ($P>0.05$)*

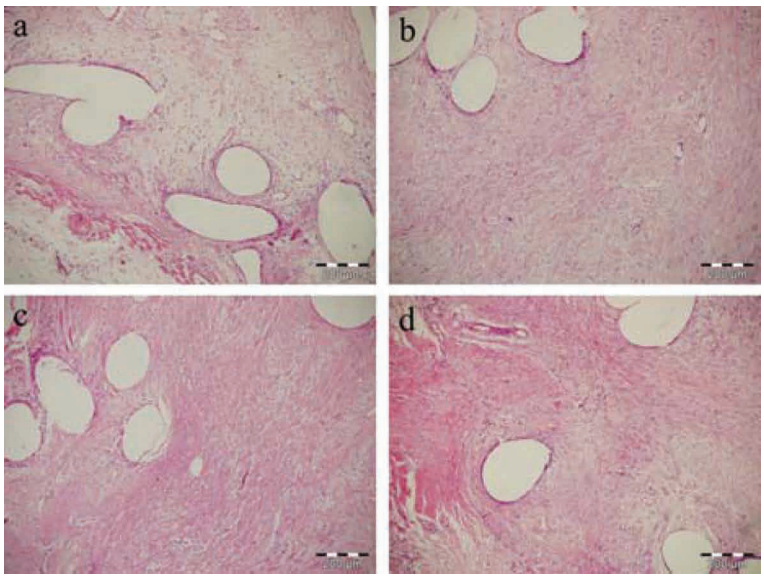

Fig 2. Fibrous tissue and healing in the DMSO (a), SF-DMSO (b), SF (c) and Control (d) groups in the areas to which the graft was applied, Hematoxilen-Eosin x 10

Şekil 2. Greft uygulanan alanlarda DMSO (a), ES-DMSO (b), ES (c) ve Kontrol (d) gruplarında fibröz doku ile iyileşme, Hematoksilen-Eosin x 10

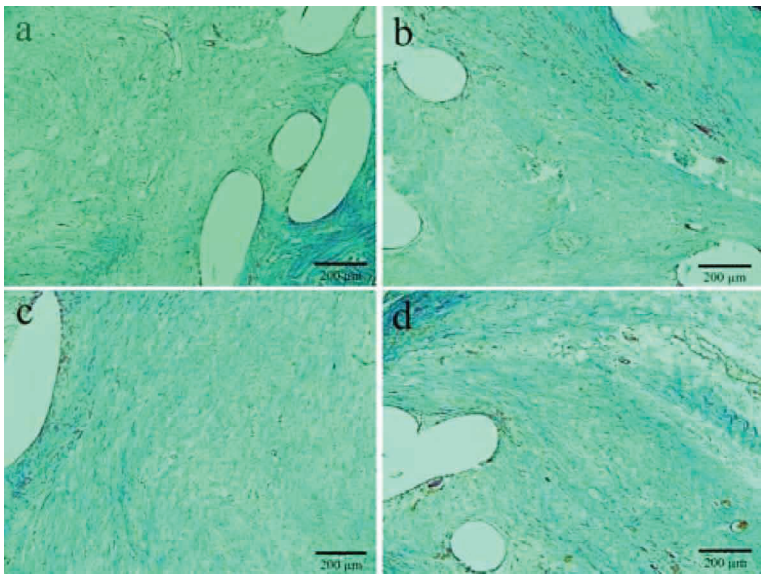

Fig 3. Fibrous tissue, collagen fiber and capillarization in the DMSO (a), SF-DMSO (b), SF (c) and Control (d) groups on the graft line. Crossman's triple stain x 10

Şekil 3. Greft hattında DMSO (a), ES-DMSO (b), ES (c) ve Kontrol (d) gruplarında kollajen lifler, kapillarizasyon, fibröz doku. Crossman'ın üçlü boyaması x 10

Table 2. *Staging according to dissection difficulty*
Tablo 2. *Diseksiyon zorluğuna göre derecelendirme*

Degree of Adhesion		**Group I**	**Group II**	**Group III**	**Group IV**
No adhesion	0	n: 8	n: 9	n: 10	n: 8
Adhesion that separated with light blunt dissection	1	n: 2	n: 1	n: -	n: 2
Adhesion that separated with aggressive blunt dissection	2	n: -	n: -	n: -	-
Adhesion that separated with sharp dissection	3	n: -	n: -	n: -	-

Healing with fibrous tissue in the graft area was observed in the DMSO group *(Fig. 1a-2a)* and fibrosis was less developed than it was in the other groups. In two of the animals from this group, it was determined that foreign body reaction and necrosis had occurred and that there was intense lymphocyte infiltration of the area to which the graft was applied. Healing with fibrous tissue was identified in the group given SF-DMSO *(Fig. 1b-2b)*. Mild mononuclear cell infiltration created primarily by lymphocytes was identified in only one animal in this group. Organization with fibrous tissue was found to be quite good in the group given SF *(Fig. 1c-2c)*. Similarly, in most of the animals in the control group, fibrosis was found to be better developed *(Fig. 1d-2d)*. In one of the animals from the control group, necrosis was observed in the grafted area and in two animals there was mild to moderate mononuclear cell infiltration.

Table 3. *Statistical results for the adhesion scale evaluation*
Tablo 3. *Yapışıklık skala değerlendirmesinin istatistiksel sonuçları*

Kruskal-Wallis Test on the Adhesion Scale	Group I	Group II	Group III	Group IV
N	10	10	10	10
Median	1.000	1.000	1.000	1.000
Av. Rank	22.0	20.0	18.0	22.0
Z	0.47	- 0.16	- 0.78	0.47

The evaluation scale results were categorized according to the visual adhesion scale reported by Jenkins et al.[13] *(Table 2)*.

As can be seen in the table, two rabbits in the first and fourth group and one rabbit in the second group had adhesion separation with light blunt dissection while there was no adhesion in the third group.

The results of the adhesion scale were evaluated non-parametrically and statistical calculations were performed with the Kruskal-Wallis test *(Table 3)*. No statistical difference was found between the groups (P=0.7337).

DISCUSSION

It has been reported that peritoneal adhesions can form due to the prosthetic mesh used to repair both ventral hernias and following any abdominal surgery including gynecological operations [1-3,7,8,11,12]. These adhesions are fibrous bands that develop between the peritoneal area where the prosthetic material is used and the serosal surface of neighboring organs or between the serosal surfaces of two different organs. The most important factors that trigger adhesion are previous operations, ischemia and foreign objects [1-8,11-13]. In this study an indirect trauma was created by forming a defect 2 cm in diameter and then creating the conditions required for adhesion by using polypropylene mesh. The formation of adhesions due to the polypropylene mesh can be explained as increased inhibition of plasminogen activators during the inflammation that occurs as a result of foreign body reaction because increased inflammation due to foreign body reaction or trauma is reported to lower fibrinolytic activity and the level of tissue plasminogen activator (tPA) even though it increases the level of type-1 and type-2 plasminogen activator inhibitor (PAI), which neutralizes the effect of tPA [7,8,12]. The fact that adhesion in all of the cases where adhesion was identified developed between the intestinal serosa and the area with the defect where polypropylene mesh was used was viewed as support of the proposed thesis.

The fact that mast cells are activated after trauma increases capillary permeability by triggering histamine and vasoactive kinins, and the result is that a seroangiotic fluid which is the basis for the formation of the fibrous bands in the peritoneal cavity begins to form. Fibrinolytic activity reportedly begins to occur three days after the trauma due to the suppressive effect of the trauma and rises above normal levels after eight days [12]. It is important to prevent adhesions during this process as they can cause intestinal obstruction, volvulus, infertility and abdominal pain. Fibrinolytics, anticoagulants, anti-inflammatory agents and a number of materials that create a physical barrier have been studied for this purpose [1-3,11,12]. Synthetic derivatives of HA esters, especially the gel form, have been used not only in a number of surgical procedures but also to prevent peritoneal adhesions in recent years [7,12,15,20,25]. Bovine synovial fluid was used for the first time in this rabbit model we created because it is easy and cheap to obtain. The concentration of HA in bovine synovial fluid is between 2-4 mg/ml and it is what gives synovial fluid its viscosity [20]. Because supernatant obtained after processing with a centrifuge was used in this study, it is very likely that this percentage was higher. As a result of the relaparotomy, a single stage-1 fibrin band approximately 0.4 cm wide and 4 cm long was identified between the center of the graft and an organ in 2 subjects from groups I and IV, and in 1 subject from group II, but no adhesions were found in any subjects from group III. Even though there was no statistical difference (P=0.7337) between the groups according to the adhesion scale results which were evaluated statistically with the Kruksal-Wallis test and viewed as nonparametric, the macroscopic findings of the relaparotomy were remarkable.

It was clear from the findings in which staging was performed according to difficulty of dissection that the fibrin band separated in all subjects with light blunt dissection. The explanation for this is probably that the fibrin band had not yet organized because of the short postoperative period. Studies have demonstrated that significant fibrous bands can be observed 10 days after peritoneal injury, reaching their highest level in 2-3 weeks and weakening as a result of remodeling in the ensuing period [5,7,8,11,12].

The results of histopathological examination revealed that the tissue which covered the graft in all of the groups was fibrous tissue. However, it was determined that the fibrosis was weaker in the DMSO group than it was in the SF-DMSO, SF and S groups. When compared in this regard, it could be said that the fibrinolytic effect of DMSO was better than SF. However, the macroscopic evaluation conducted with relaparotomy revealed no adhesions in any of the subjects given SF. Even though it was not statistically significant in preventing postoperative adhesion, SF was more effective than the other three groups from a clinical perspective. In light of these results, SF did have relative success in preventing adhesion even though its fibrinolytic effect was weak. One explanation might be that this is the result of SF serving to create a barrier and acting as a lubricant between the graft material and the serosa of internal organs due to its high viscosity.

The side of the graft facing the peritoneum in all of the subjects evaluated macroscopically with relaparotomy was covered with a shiny tissue consistent with the peritoneum. Experimental and clinical studies have demonstrated that

no matter how large a defect is it is repaired within 3-5 days by mesothelial cells from neighboring areas [2,5,7-13]. It is claimed that the rapid healing potential of the peritoneum and its unique physiological characteristics play an important role both in the formation of intraabdominal adhesions and their prevention [5-8,12]. The results of the histopathological evaluation in this study demonstrate that the surface of the graft was repaired homogenously with collagen fibers, capillarization and fibrous tissue.

Alkan et al.[7] reported that DMSO administered to rabbits in a 1 g/kg dose was effective in preventing postoperative adhesion and that immature fibrosis did develop. In the study that we did, DMSO (1.5 g/kg) was administered intraperitoneally. Histopathological examination of the tissue samples that were taken showed that fibrosis had developed to a certain degree but that it was weaker than it was in the other groups. However, foreign body reaction, lymphocyte infiltration and necrosis were found to have developed in two of the subjects. In light of the evaluation between the groups, adhesion was identified in one or two subjects in all of the groups except for the SF group. This is noteworthy from a macroscopic perspective even though it was not statistically significant as it does show that SF was effective in preventing the occurrence of adhesion without suppressing the fibrosis that is required for injuries to heal.

Although any allergic findings are not determined as clinically and histopathologically, the further detailed studies including allergic tests are needed in order to apply in clinical practice.

In light of the macroscopic and histopathological findings obtained from relaparotomy and the statistical analysis of these findings, it was concluded that SF is effective in preventing adhesions even though it does not suppress fibrosis, which is necessary for injuries to heal, as much as DMSO does Based on these results, we could say that organic formulations of HA, such as synovial fluid obtained by more modern methods, and not just the synthetic derivations can be used to prevent postoperative adhesions and that there is a need for more advanced studies to be conducted for clinical procedures.

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