Cerrahpaşa Med J 2023; 47(3): 279-284 ORIGINAL ARTICLE

# Composing an Adhesion Barrier Using Hyaluronic Acid and Carboxymethylcellulose to Prevent Mediastinal Adhesion

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***Abstract***

**Objective:** Remediastinal intervention is an indispensable procedure to assess mediastinal lymph node metastasis after induction chemotherapy in patients with non-small cell lung cancer. Remediastinal interventions can be a difficult procedure because adhesions from a prior mediastinoscopy may reduce the surgeon's field of view and may cause difficulty in diagnosing a lymph node, which causes suspicion about invasion. There are several adhesion barrier procedures, which were used to prevent postoperative adhesions, but none of them provided remarkable results. There are studies including abdominal, gynecologic, and neurochirurgic surgery; however, there is no sufficient study regarding mediastinum. In this study, we have explored the role of hyaluronic acid and carboxymethylcellulose in preventing mediastinal adhesion.

**Methods:** In our study, 21 New Zealand-type male and female rabbits—each with a weight of 2500-3500 g—were used. Three groups, each including 7 rabbits, were set up using randomized sampling method. Mediastinal dissection was performed in the first group and Seprafilm® was used to build adhesion inhibition. Mediastinal dissection was performed in the second group, and 0.9% NaCl was used to build adhesion inhibition. In the control group, all layers were sutured primarily after mediastinal dissection. The rabbits were sacrificed after 30 days and each group was compared with the control group, using macroscopic and microscopic adhesion criteria.

**Results:** According to the results of our study, Seprafilm® was found to be statistically efficient in preventing and decreasing adhesion in mediastinum ($P < .01$ in macroscopic criteria, $P < .05$ in inflammation, and vascular proliferation criteria).

**Conclusion:** Seprafilm® can be used as an adhesion barrier in prevention of adhesions that develop as a result of surgery.

**Keywords:** Mediastinoscopy, mediastinal adhesion, remediastinoscopy, sodium hyaluronate–carboxymethylcellulose

## Introduction

Evaluating mediastinal lymph nodes is crucial in determining patient survival.[1] Surgical resection after neoadjuvant treatment prolongs survival in patients with advanced lung cancer. However, mediastinal lymph nodes should be reevaluated before this surgical procedure.[2,3] Remediastinal interventions are necessary due to its high specificity in patients with shrinking mediastinal lymph nodes after neoadjuvant therapy. The technical difficulty of remediastinal interventions is due to the fibrosis and adhesions in the pretracheal and retrovascular areas caused by the inflammatory process related to the previous procedure. This prevents the advancement of the mediastinoscope, narrows the surgeon's working field, causes unwanted bleeding, and ultimately increases morbidity and decreases the sensitivity of the procedure.[4]

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Various barrier methods have been tried to prevent these adhesions, but no significant success has been achieved. Seprafilm®, the most commonly used membrane barrier, is a bioresorbable material composed of hyaluronic acid and carboxymethylcellulose. Studies have focused on abdominal surgeries and gynecologic and neurosurgical interventions, but studies focusing on the mediastinum are insufficient.

In this study, we investigated the role of sodium hyaluronate and carboxymethyl cellulose in preventing adhesions in the mediastinum.

## Methods

The study used 21 New Zealand rabbits of both sexes, weighing between 2500 and 3500 g. Rabbits were divided into 3 groups by random sampling [Seprafilm® (Genzyme Company, Ridgefield, NJ, USA), isotonic, and control group], with 7 rabbits in each group. We use 0.9% NaCl (isotonic) because we wanted to use a simple material that can only form a barrier, comparable to hyaluronic acid and carboxymethylcellulose. The simplest example we found was 0.9% NaCl. At the same time, crystalloid solutions can be used to prevent adhesions.[5]

The total duration of the study was determined as 2 months. Before the procedure, the rabbits were observed for 10 days in separate cages, and their health status was monitored. Rabbits that died during this observation period were not included in the study. They were fed with routine food and water during the whole period. No death or infection in the surgical area was observed in the rabbits included in the study. All animals were subjected to humanistic treatment following the Guide for the Care and Use of Laboratory Animals. There is no ethics committee approval because there was no ethical committee existence in 2008, which is the year of our study.

All operations were performed under semisterile conditions in the animal laboratory. Ketamine hydrochloride 50 mg/kg and xylazine hydrochloride 5 mg/kg were used intramuscularly for anesthesia. The surgical procedure lasted an average of 15 minutes. The researchers monitored anesthesia-related side effects by observing cardiac mechanical activity and oxygen saturation, and any complications were tried to be eliminated by intervention. The operation was performed in sterile areas. The necks of the rabbits in all 3 groups were shaved and wiped with povidone–iodine solution, and a 2-cm horizontal skin incision was made in the cervical region, half a centimeter above the sternum. The anterior region of the trachea was reached by passing the strep muscles with blunt dissection made from the midline. The anterior and lateral area of the trachea was dissected until the carina. In the first group (Seprafilm® group), Seprafilm® was placed in the anterior part of the trachea from the hyoid level to the carina. In the second group, the isotonic group, only saline was applied to the anterior part of the trachea. In the third group, the control group, closure was performed without any barrier agent following dissection. In all groups, the strep muscles were closed over the trachea with 6/0 absorbable multifilament braided suture material. The skin was closed with 4-0 absorbable multifilament braided suture material. Animals were started to be fed food and water at the fourth postoperative hour.

Thirty days later, after all, 3 groups were sacrificed under anesthesia, a skin incision was made in the same place, the trachea was explored to evaluate the degree of adhesion, and visual scoring was performed. Then, a partial sternotomy was performed without disrupting the integrity of the strep muscles, and the segment of the trachea between the infrahyoid and carina was removed together with the strep muscles. The preparations were numbered in such a way that it was not clear which group they belonged to and were evaluated macroscopically and microscopically by 2 different pathologists. The specimens were stored in 10% neutral buffered formalin. The tissues were leveled and sampled and placed in tissue tracing. The tissues were embedded in paraffin, and 3µ sections were prepared and stained with hematoxylin–eosin. Histopathologically, increased collagen tissue, fibrosis, degenerative muscle changes, inflammation, vascular proliferation, inflammatory cells, multinuclear giant cells, and granulation tissue were evaluated. Some macroscopic and microscopic scores were used to evaluate adhesions in the preparations.

The macroscopic evaluation was performed in a double-blind manner using the adhesion scoring system used by Mazuji et al[6] and Erkol et al.[7] Accordingly, no adhesions were scored as score 0, thin or narrow adhesions that could be easily separated were scored as score 1, thick adhesions limited to 1 area were scored as score 2, thick and wide adhesions were scored as score 3, and thick and wide adhesions extending to the wall anteriorly and posteriorly to the organs were scored as score 4.

The scoring system of Hooker et al[8] was applied in the double-blind microscopic fibrosis evaluation. Accordingly, the absence of fibrosis was evaluated as score 0, minimal loose fibrosis as score 1, moderate fibrosis as score 2, and florid dense fibrosis as score 3.

The scoring system of Hooker et al[8] was again used in the double-blind microscopic evaluation of inflammation. Absence of inflammation was scored as score 0; foreign body-type giant cells, rare scattered lymphocytes, and plasma cells were scored as score 1; foreign body-type giant cells with an increased number of lymphocytes, neutrophils, eosinophils, and plasma cells were scored as score 2; and the presence of many mixed inflammation cells and microabscesses were scored as score 3.

In addition, endothelial proliferation was also evaluated and scored in a double-blind manner since neovascularization should be considered in addition to inflammatory cells to evaluate granulation tissue microscopically. Accordingly, the absence of vascular proliferation was considered a score 0, mild endothelial proliferation a score 1, moderate endothelial proliferation a score 2, and intense endothelial proliferation a score 3.

Kruskal–Wallis and Mann–Whitney *U*-tests were used for statistical data analysis. $P < .05$ was considered significant.

## Results

### Seprafilm Group

On exploration in rabbit I, a thin fibrous band was seen on the trachea, which was easily peeled off and recorded as score 1. Microscopically, a small amount of fibrosis was observed between the muscle fibers (score 1), while inflammation and vascular proliferation were not seen (score 0). The trachea was easily explored in rabbit II, and no adhesions were seen (Figure 1). Microscopically, a regular tracheal structure was observed. All scores were recorded as 0 (Figure 2). In rabbit III and rabbit IV, a dissection without adhesions was performed in the same manner.

Microscopically, the trachea and surrounding tissues were regular. All scores were recorded as 0. In rabbit V, a minimal fibrotic band was seen on the trachea but was easily peeled off; the score was recorded as 1. Microscopically, fibrosis, inflammation, and endothelial proliferation were not seen; all scores were recorded as 0. In rabbit VI, no adhesions were observed on the trachea (score 0), while microscopically, minimal fibrosis was seen

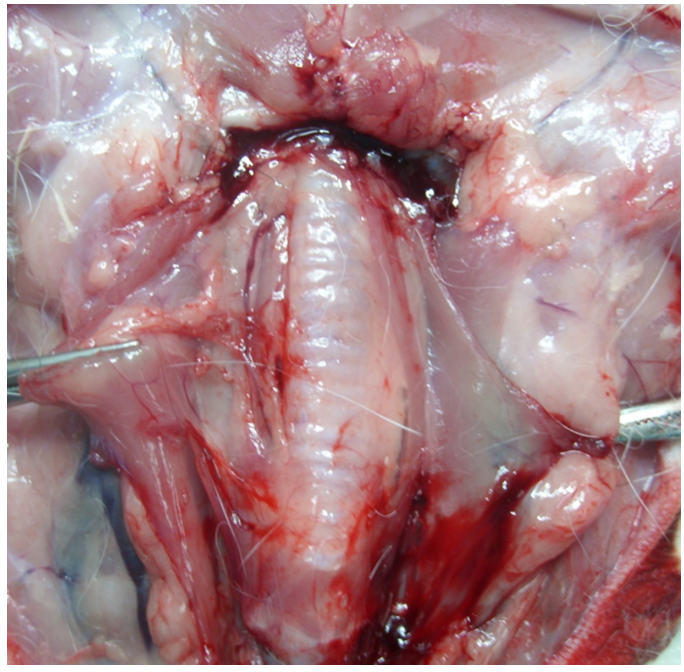

**Figure 1.** Trachea easily dissected due to lack of adhesion in rabbit II.

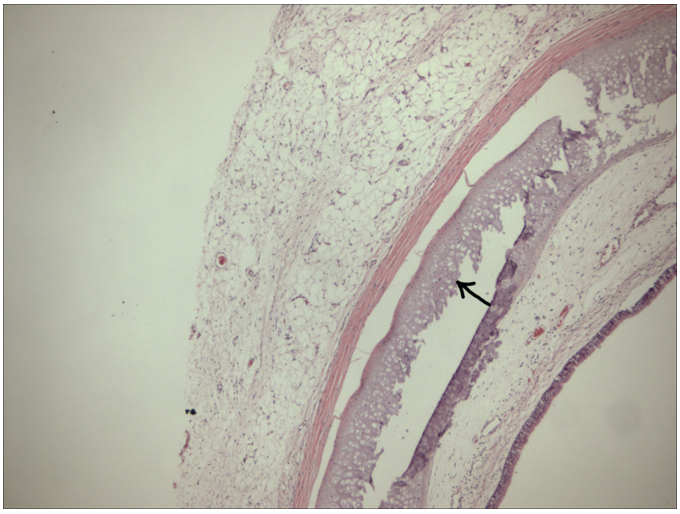

**Figure 2.** Microscopically ordered structure in rabbit II (hematoxylin–eosin ×40) (The cartilage layer is marked with an arrow).

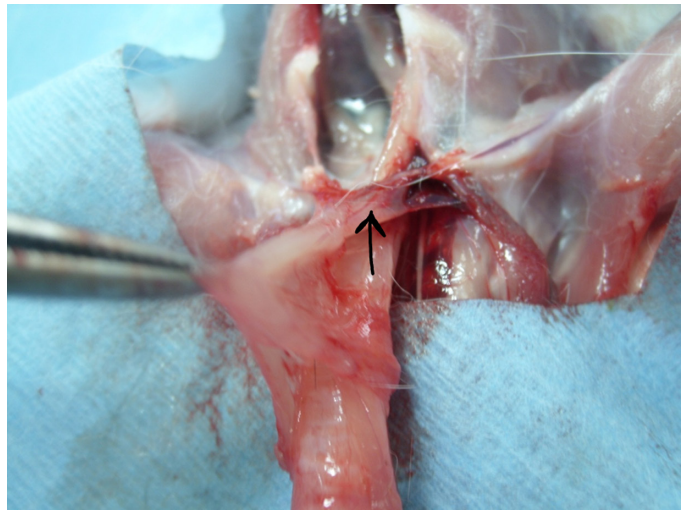

**Figure 3.** Macroscopically diffuse adhesions on the trachea in rabbit V of the isotonic group (fibrotic adhesions are marked with an arrow).

(score 1). Inflammation cell and endothelial proliferation were not observed (scores 0 and 0). In rabbit VII, a minimal fibrotic band was seen on the trachea that was easily peeled off and recorded as score 1. Microscopically, fibrosis, inflammation, and endothelial proliferation were not seen, and all scored as 0.

**Isotonic Group**

In rabbit I, the muscles over the trachea were too fixed to be detached from the trachea. The trachea could not be opened, and the score was recorded as 4. Microscopically, the fibrosis score was 2. The inflammation score was 3 due to increased lymphocytes, eosinophils, and neutrophils; the increased vascular proliferation score was 2. In rabbit II, a minimal fibrotic band was seen on the trachea, which was easily peeled off, and the score was recorded as 1. Microscopically, fibrosis, inflammation, and endothelial proliferation were not seen; all were scored as 0. In rabbit III, thick fibrotic plaques were seen on the trachea, especially in the lower tracheal regions; the score was recorded as 2. However, microscopically, fibrosis, inflammation, and endothelial proliferation were not observed; all were scored as 0. In Rabbit IV, a minimal fibrotic band was seen on the trachea, easily peeled off; the score was recorded as 1. Microscopically, fibrosis, inflammation, and endothelial proliferation were not seen; all were recorded as score 0. In rabbit V, macroscopically diffuse adhesions were seen macroscopically on the trachea on exploration and scored as 3 (Figure 3). Microscopically, diffuse fibrosis (score 3), sparse inflammatory cells accompanied by foreign body giant cells (score 2), and mild endothelial proliferation (score 1) were seen in the structures anterior to the trachea (Figure 4). In rabbit VI, macroscopically, no obvious adhesion was seen anterior to the trachea, but localized dense adhesion was seen around the carina and was recorded as score 2. Microscopically, minimal fibrosis, rare inflammatory cells, and endothelial proliferation were seen and scored 1 on each scale. In rabbit VII, a thick fibrotic plaque, again confined to a specific location, was seen and recorded as macroscopic score 2. Microscopically, minimal fibrosis, rare inflammatory cells, and endothelial proliferation were seen (scores 1, 1, and 1).

**Control Group**

In rabbit I, a minimal fibrotic band was seen on the trachea but was easily peeled off; it was recorded as score 1. Microscopically, fibrosis, inflammation, and endothelial proliferation were not observed, and all were graded as score 0. In rabbit II, no exploration was possible due to adhesions on the trachea from the previous operation, and the score was recorded as 4. Microscopically, loose fibrosis (score 1), diffuse inflammation consisting of lymphocytes, eosinophils, and polymorphous nucleocytes (score 3), and moderate endothelial proliferation (score 2) (Figure 5). In rabbit III, diffuse adhesions were seen on the trachea; the score was recorded as 3 (Figure 6). Microscopically, score 2 fibrosis was observed, while the inflammation score was evaluated as 1 due to sporadic lymphocytes. Mild (score 1) endothelial proliferation was seen. In rabbit IV, extensive adhesions were seen on the trachea (score 3). Microscopically, score 2 fibrosis, sparse lymphocytes (score 1), and mild endothelial proliferation (score 1) were seen. In rabbit V, dissection revealed very thick fibrotic plaques in the lower parts of the trachea, which were macroscopically scored as score 2. Microscopically, moderate fibrosis was recorded as score 2, while inflammation scale and endothelial proliferation were evaluated as 1. In rabbit VI, a minimal

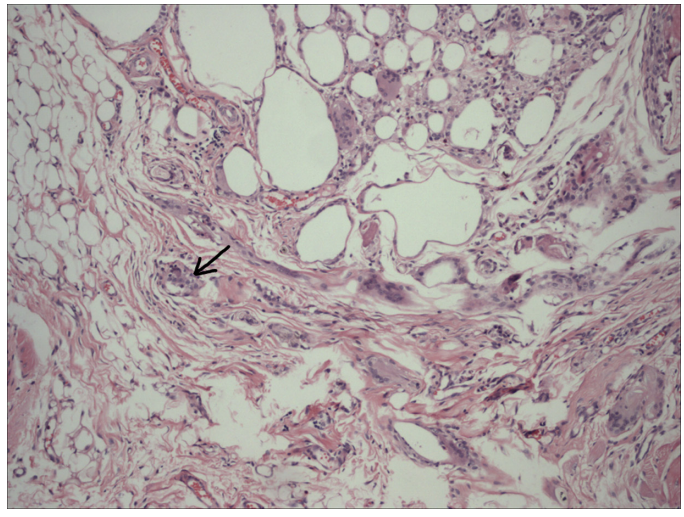

**Figure 4.** Foreign body giant cells and rare inflammatory cells microscopically in rabbit V of the isotonic group (hematoxylin–eosin ×100) (a foreign body giant cell is marked with an arrow).

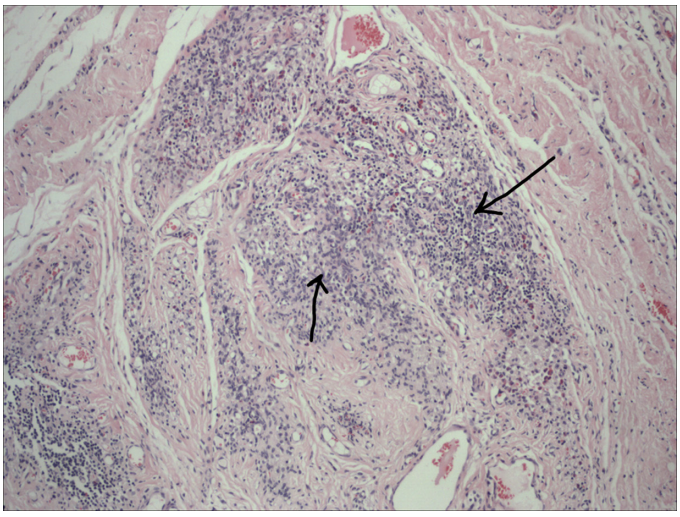

**Figure 5.** Intense lymphocyte, eosinophil, and polymorph nucleoside infiltration (marked with arrows) in the pretracheal area and increased vascular proliferation between them in microscopic examination in rabbit II of the control group (hematoxylin–eosin ×100).

fibrotic band was seen on the trachea that was easily peeled off; the score was recorded as 1. Microscopically, fibrosis, inflammation, and endothelial proliferation were not seen; all were scored as 0. In rabbit VII, a minimal fibrotic band was seen on the trachea that was easily peeled off (score 1). Microscopically, minimal fibrosis, rare inflammatory cells, and endothelial proliferation were seen; all were considered score 1.

### Statistical Analysis

All 3 groups were evaluated among themselves, and statistical results were obtained with the Kruskal–Wallis test. There was a statistically significant difference between the groups regarding macroscopic scale scores ($P < .01$). Similarly, a statistically significant difference was found in terms of inflammation scale and endothelial proliferation scores ($P < .05$). However, there was no statistically significant difference between the groups regarding fibrosis scale scores ($P > .05$) (Table 1).

Mann–Whitney *U*-test showed no statistically significant difference between control and isotonic groups in terms of macroscopic scale, fibrosis scale, inflammation, and endothelial proliferation scores ($P > .05$) (Table 2).

In the Mann–Whitney *U*-test, macroscopic scale scores of the control group were statistically significantly higher than the Seprafilm group ($P < .01$). The control group's inflammation and endothelial proliferation scale scores were statistically significantly higher than the Seprafilm group ($P < .05$). There was no statistically significant difference between the control and Seprafilm groups in terms of fibrosis scale scores ($P > .05$) (Table 3).

Again with the Mann–Whitney *U*-test, macroscopic scale scores of the isotonic group were statistically significantly higher than the Seprafilm group ($P < .01$). There was no statistically significant difference between Seprafilm and isotonic groups in terms of fibrosis, inflammation, and endothelial proliferation scale scores ($P > .05$) (Table 4).

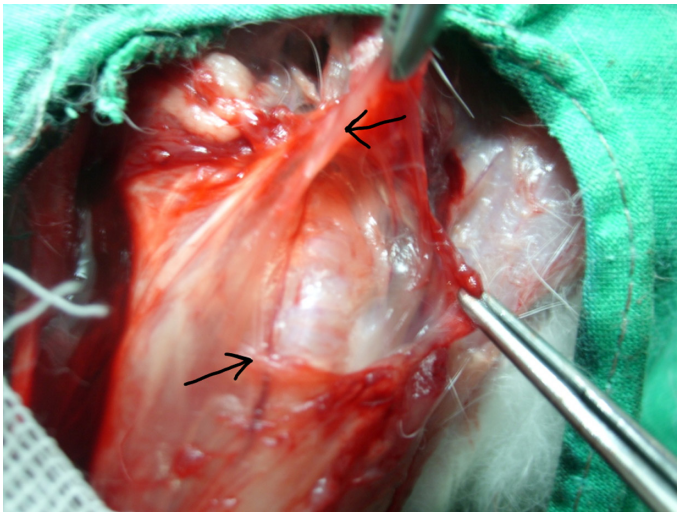

**Figure 6.** Widespread adhesion (marked with arrows) on the trachea in rabbit III of the control group.

**Table 1.** Comparison of 3 Groups in Terms of Score via Kruskal–Wallis Test

| | Control Group | | Isotonic Group | | Seprafilm Group | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | *P* |
| Macroscopic scale | 2.14 | 1.21 | 2.14 | 1.07 | 0.43 | 0.53 | .006 |
| Fibrosis scale | 1.14 | 0.90 | 1.00 | 1.15 | 0.29 | 0.49 | .174 |
| Inflammation scores | 1.00 | 1.00 | 1.00 | 1.15 | 0.00 | 0.00 | .029 |
| Endothelial proliferation scores | 0.86 | 0.69 | 0.71 | 0.76 | 0.00 | 0.00 | .026 |

**Table 2.** Comparison of Isotonic and Control Groups in Terms of Score via Mann–Whitney *U*-Test

| | Control Group | | Isotonic Group | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | *P* |
| Macroscopic scale | 2.14 | 1.21 | 2.14 | 1.07 | 1.00 |
| Fibrosis scale | 1.14 | 0.90 | 1.00 | 1.15 | .710 |
| Inflammation scores | 1.00 | 1.00 | 1.00 | 1.15 | .902 |
| Endothelial proliferation scores | 0.86 | 0.69 | 0.71 | 0.76 | .710 |

**Table 3.** Comparison of Control Group and Seprafilm Group in Terms of Score via Mann–Whitney *U*-Test

| | Control Group | | Seprafilm Group | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | *P* |
| Macroscopic scale | 2.14 | 1.21 | 0.43 | 0.53 | .007 |
| Fibrosis scale | 1.14 | 0.90 | 0.29 | 0.49 | .097 |
| Inflammation scores | 1.00 | 1.00 | 0.00 | 0.00 | .026 |
| Endothelial proliferation scores | 0.86 | 0.69 | 0.00 | 0.00 | .026 |

**Table 4.** Comparison of Isotonic and Seprafilm Groups in Terms of Score via Mann–Whitney ***U***-Test

| | Isotonic Group | | Seprafilm Group | | |
|---|---|---|---|---|---|
| | **Mean** | **SD** | **Mean** | **SD** | ***P*** |
| Macroscopic scale | 2.14 | 1.07 | 0.43 | 0.53 | .004 |
| Fibrosis scale | 1.00 | 1.15 | 0.29 | 0.49 | .259 |
| Inflammation scores | 1.00 | 1.15 | 0.00 | 0.00 | .073 |
| Endothelial proliferation scores | 0.71 | 0.76 | 0.00 | 0.00 | .073 |

## Discussion

Surgical resection after neoadjuvant treatment in advanced lung cancer cases prolongs patient survival; however, mediastinal lymph nodes should be reevaluated for the patient's suitability for surgical treatment. It has been emphasized that lymph node involvement is the only effective parameter in survival compared to other parameters.[3] However, adhesions due to previous mediastinoscopy narrow the surgeon's working area and create difficulty in lymph node differentiation in an invasive view. Considering that lymph node involvement is the most influential parameter in survival, various methods have been tried to eliminate these obstacles.

Physical barriers that prevent adhesion can be categorized into 2 main groups: liquid and membrane. Many membrane barriers have been used to prevent postoperative adhesions. These include membrane composed of hyaluronic acid and carboxymethylcellulose (Seprafilm®), membrane developed from polytetrafluoro ethylene, oxidized regenerated cellulose, N, O-carboxymethyl chitosan, Synvisc, polyethyleneglycol/polylactic acid films, human amniotic membrane, Adcon-P, TNP-470, and PLLA-PEG copolymer films.[9-17]

Seprafilm® is a bioresorbable material composed of hyaluronic acid and carboxymethylcellulose. It has been used in abdominal surgeries since the early 1990s to reduce postoperative adhesions.[17,18,19] Hyaluronic acid is a natural anionic polysaccharide. It is found in connective tissue, skin, cartilage, and synovial fluid. It is the main component of the extracellular matrix. It is hydrophilic with a very high molecular weight. It has a viscoelastic structure with properties of the coating and lubricating serosal surfaces. Carboxymethylcellulose is an anionic polysaccharide. It is a cellulose derivative containing groups that make the polymer more hydrophilic. Hyaluronic acid–carboxymethylcellulose is an effective, nontoxic, nonimmunologic, and biologically appropriate material for reducing the incidence and prevalence of severe postoperative adhesions. Seprafilm® transforms completely into a hydrophilic gel approximately 24 to 48 hours after application. The hyaluronic acid component is completely cleared from the body within 28 days. Carboxymethylcellulose is cleared to a lesser extent. Although the risk of systemic side effects is low, its effectiveness is high. It can be used even when there is blood in the environment. Despite all its efficacy, some problems have been identified in its use. Since it is in the form of a film, its use requires special skill, and it cannot be used in laparoscopic surgery. Although rare, some cases of peritonitis due to Seprafilm® have been reported. It is also expensive, which is a significant disadvantage. Although there is not much literature on preventing surgical adhesions in the mediastinum, there are studies on using anti-adhesion barriers, especially in abdominal and pelvic surgeries.[20,21] To prevent adhesions in the current approach, minimally invasive surgical techniques should be selected, the inflammatory response should be reduced, coagulation should be inhibited, fibrinolysis should be stimulated, and adhesion-prone surfaces should be separated. The ideal physical membrane barrier should not affect wound healing, should not stimulate fibrosis formation, should not be metabolized during the adhesion formation phase, and should be effective in the presence of blood and foreign bodies.

In a 1996 multicenter study by Diamond et al,[21] Seprafilm® was found to be effective in reducing adhesions after gynecologic surgery compared to second-look laparoscopy in 127 patients who underwent myomectomy operations. In addition, in a 1997 multicenter study by Beck et al,[22] Seprafilm® was effective and safe in reducing the incidence of adhesions in standard colectomy and ileal J-pouch anastomosis + loop ileostomy operations performed after ileostomy closure. These findings are similar to the results of our study.

Although Seprafilm® is not recommended for endoscopic procedures due to its difficulty in use, Khaitan et al,[23] developed a new method of Seprafilm® placement after laparoscopic adhesiolysis in patients with chronic pelvic pain due to postoperative adhesions. In this case, the protective paper on Seprafilm® was rolled without removing it, the trocar was placed in the trocar removed through the port, the trocar was sent through the port again, and the membrane was opened in the abdomen. The protective paper was opened over the planned area, and the membrane was placed endoscopically. A similar method was described by Sano R et al.[24] We think that this method can also be used in the mediastinoscopy procedure.

In a study by Tsapanos et al,[25] Seprafilm® was used to prevent and treat endometrial synechiae. In the study by Kobayashi et al,[26] the use of Seprafilm® in patients undergoing rehepatectomy was thought to reduce the risk of postoperative morbidity concerning the reduced technical difficulty in lysis of the adhesion. The results obtained from these studies are similar to the results of our study.

Two important studies investigating the role of barrier materials in preventing adhesions in mediastinum have been reported in Turkey. In the experimental study by Solak et al,[27] the adhesion prevention efficacy of Hyalan B Gel (Sepragel®) material was measured, and the efficacy of the barrier material was found to be statistically significant. Unlike our study, only microscopic scoring systems were used, and no macroscopic evaluation was performed in this study. In addition, it was not evaluated whether any material to be placed between the tissues would have a Sepragel®-like efficacy. A similar study was conducted by Büyükkale S et al,[28] and similar results were obtained with very similar methods to our study; differently, a group other than the control and Seprafilm group was not defined.

Although the number of subjects was low in our study, the statistical results were significant. Although the scales varied in all 3 groups, no macroscopically advanced scores were recorded in the Seprafilm® group, and no granulation tissue was observed microscopically. Overall, there was a significant difference between the groups, especially in terms of macroscopic adhesions. On the other hand, there may be various reasons for the lack of statistical difference between the groups in the scores obtained regarding fibrosis. Fibrosis is a process observed later than granulation tissue; the significant results obtained in granulation tissue in our study may suggest that a longer time should be allowed for fibrosis to develop. In our study, remediastinoscopy was performed on the 30th day after the first operation. In addition, the animal study did not use neoadjuvant chemotherapy, another cause of fibrosis encountered in remediastinoscopies. In addition, the difference between a rabbit and human anatomy, the looser and easier dissection of rabbit tissue compared to human tissue, and therefore almost no bleeding during the operation is another factor that caused the fibrosis

scale to be recorded as low. Since mediastinoscopies performed in humans will have some bleeding and this extravasated blood will contribute to fibrosis during the organization process, it should be taken into consideration that a similar experiment on humans may provide more efficient results on fibrosis development when applying the results of our research to real cases.

Our study revealed a noteworthy distinction between the isotonic group and the Seprafilm® group, prompting us to investigate the efficacy of nonspecific materials in preventing adhesions between anatomical layers. Based on macroscopic adhesion scoring, we concluded that Seprafilm® proved significantly more effective in preventing adhesions. In support of this, no significant difference was found between the isotonic group and the control group on any scale, and it was thought that the barrier efficiency of isotonic or similar material was insufficient. There was a macroscopically significant difference between the control group and the Seprafilm® group. In microscopic evaluation, the lower scores of the Seprafilm® group, especially in terms of inflammation and vascular proliferation, were statistically significant.

## Conclusion

Our study found a statistically significant difference between the Seprafilm® group and the control groups regarding macroscopic adhesion scoring and granulation tissue scoring. Seprafilm® is a suitable barrier with minimal side effects and is effective in preventing adhesion, as proven in various studies. Although Seprafilm® is a difficult and expensive material to use, these charcteristics can be ignored because it facilitates remediastinal interventions.

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**Informed Consent:** N/A.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – A.M.A.; Design A.D.; Supervision – K.K.; Resources – A.M.A.; Materials – A.M.A.; Data Collection and/or Processing – F.Ş.; Analysis and/or Interpretation – R.R., B.Ö.; Literature Search I – A.M.A.; Writing Manuscript – A.M.A.; Critical Review – E.E.

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## References

1. De Waele M, Hendriks J, Lauwers P, et al. Nodal status at repeat mediastinoscopy determines survival in non-small cell lung cancer with mediastinal nodal involvement, treated by induction therapy. *Eur J Cardiothorac Surg*. 2006;29(2):240-243. [CrossRef]
2. Van Schil P, van der Schoot J, Poniewierski J, et al. Remediastinoscopy after neoadjuvant therapy for non-small cell lung cancer. *Lung Cancer*. 2002;37(3):281-285. [CrossRef].
3. Stamatis G, Fechner S, Hillejan L, Hinterthaner M, Krbek T. Repeat mediastinoscopy as a restaging procedure. *Pneumologie*. 2005; 59(12):862-866. [CrossRef]
4. De Leyn P, Stroobants S, De Wever W, et al. Prospective comparative study of integrated positron emission tomography-computed tomography scan compared with remediastinoscopy in the assessment of residual mediastinal lymph node disease after induction chemotherapy for mediastinoscopy-proven stage IIIA-N2 non-small-cell lung cancer: a Leuven Lung Cancer Group Study. *J Clin Oncol*. 2006; 24(21):3333-3339. [CrossRef].
5. Hellebrekers BWJ, Trimbos-Kemper GCM, van Blitterswijk CA, Bakkum EA, Trimbos JBMZ. Effects of five differents barrier materials on postsurgical adhesion formation in the rat. *Hum Reprod*. 2000; 15(6):1358-1363. [CrossRef]
6. Mazuji MK, Kalambaheti K, Pawar B. Prevention of adhesions with polyvinylpyrrolidone. *Arch Surg*. 1964;89(6):1011-1015. [CrossRef]
7. Erkol H, Perek S, Tunalı H, Sanal İ. Ratlarda karın içi yapışıkların önlenmesinde intraperitoneal heparin ve sodyum karboksimetilse llülozun etkileri. *Çağdaş Cerrahi Derg*. 1993;7:47-51.
8. Hooker GD, Taylor BM, Driman DK. Prevention of adhesion formation with use of sodium hyaluronate-based bioresorbable membrane in a rat model of ventral hernia repair with polypropylene mesh--a randomized, controlled study. *Surgery*. 1999;125(2):211-216. [CrossRef]
9. Lee JH, Go AK, Oh SH, Lee KE, Yuk SH. Tissue anti-adhesion potential of ibuprofen-loaded PLLA-PEG diblock copolymer films. *Biomaterials*. 2005;26(6):671-678. [CrossRef]
10. Skinner KC, Colt MJ, Carver RL, Burns JW. Evaluations of HAL-F bioresorbable membrane for adhesion reduction in the rat cecal abrasion model. *Am Fertil Soc*. 1992;579:Abstract P-063.
11. Zhou J, Elson C, Lee TD. Reduction in postoperative adhesion formation and re-formation after an abdominal operation with the use of N, O - carboxymethyl chitosan. *Surgery*. 2004;135(3):307-312. [CrossRef].
12. Szabo A, Haj M, Waxsman I, Eitan A. Evaluation of seprafilm and amniotic membrane as adhesion prophylaxis in mesh repair of abdominal wall hernia in rats. *Eur Surg Res*. 2000;32(2):125-128. [CrossRef]
13. Oncel M, Remzi FH, Senagore AJ, Connor JT, Fazio VW. Application of Adcon-P or Seprafilm in consecutive laparotomies using a murine model. *Am J Surg*. 2004;187(2):304-308. [CrossRef]
14. Felemovicius I, Bonsack ME, Hagerman G, Delaney JP. Prevention of adhesions to polypropylene mesh. *J Am Coll Surg*. 2004;198(4): 543-548. [CrossRef]
15. Chiang SC, Cheng CH, Moulton KS, Kasznica JM, Moulton SL. TNP-470 inhibits intraabdominal adhesion formation. *J Pediatr Surg*. 2000;35(2):189-196. [CrossRef]
16. Zieren J, Neuss H, Ablassmaier B, Müller JM. Adhesions after intraperitoneal mesh repair in pigs: prolene" vs. Vypro". *J Laparoendosc Adv Surg Tech A*. 2002;12(4):249-252. [CrossRef]
17. Rodgers K, Cohn D, Hotovely A, Pines E, Diamond MP, diZerega G. Evaluation of polyethylene glycol/polylactic acid films in the prevention of adhesions in the rabbit adhesion formation and reformation sidewall models. *Fertil Steril*. 1998;69(3):403-408. [CrossRef]
18. Kling J. Genzyme's Seprafilm gets FDA marketing nod. *Nat Biotechnol*. 1996;14(5):572. [CrossRef]
19. Guo Y, Zhu Q, Chen S, et al. Effect of sodium hyaluronate-arboxyce llulose membrane (Seprafilm®) on postoperative small bowel obstruction: a meta-analysis. *Surgery*. 2021;169(6):1333-1339. [CrossRef]
20. Hajibandeh S, Hajibandeh S, Saeed S, Bird J, Kannappa L, Ratnayake I. Effect of hyaluronate-based bioresorbable membrane (Seprafilm) on outcomes of abdominal surgery: a meta-analysis and trial sequential analysis of randomised controlled trials. *Update Surg*. 2022;74(3):865-881. [CrossRef]
21. Diamond MP. Reduction of adhesions after uterine myomectomy by Seprafilm membrane (HAL-F): a blinded, prospective, randomized, multicenter clinical study. Seprafilm adhesion study group. *Fertil Steril*. 1996;66(6):904-910. [CrossRef]
22. Beck DE. The role of Seprafilm bioresorbable membrane in adhesion prevention. *Eur J Surg Suppl*. 1997;577(577):49-55.
23. Khaitan E, Scholz S, Richards WO. Laparoscopic adhesiolysis and placement of Seprafilm: a new technique and novel approach to patients with intractable abdominal pain. *J Laparoendosc Adv Surg Tech A*. 2002;12(4):241-247. [CrossRef]
24. Sano R, Ota Y, Tanaka T, Suzuki S, Shimoya K, Shiota M. A new technique for Seprafilm®that can be practiced with a 5-mm Trocar. *Gynecol Minim Invasive Ther*. 2021;10(3):168-170. [CrossRef]
25. Tsapanos VS, Stathopoulou LP, Papathanassopoulou VS, Tzingounis VA. The role of Seprafilm bioresorbable membrane in the prevention and therapy of endometrial synechiae. *J Biomed Mater Res*. 2002;63(1):10-14. [CrossRef]
26. Kobayashi Y, Shindoh J, Okubo S, et al. Hyaluronic acid/carboxymethyl cellulose-based adhesion barrier reduces surgical difficulty and complication in repeat hepatectomy. *HPB (Oxford)*. 2021;23(6): 907-914. [CrossRef]
27. Solak O, Esme H, Sirmali M, et al. Achieving efficient anti-adhesion in re-mediastinoscopy: an experimental study in rats. *Thorac Cardiovasc Surg*. 2008;56(3):158-161. [CrossRef]
28. Büyükkale S, Çıtak N, İşgörücü Ö, Sayar A. A bioabsorbable membrane (Seprafilm®) may prevent postoperative mediastinal adhesions following mediastinoscopy: an experimental study in rats. *Int J Clin Exp Med*. 2015;8(7):11544-11548.