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ORIGINAL ARTICLE / ÖZGÜN MAKALE

Investigation of the effects of different drugs on the prevention of intrapleural adhesion in a rat model

Farklı ilaçların intraplevral yapışıklığın önlenmesindeki etkilerinin sıçan modelinde araştırılması

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ABSTRACT

Background: The aim of this study was to investigate the antifibrinolytic and anti-inflammatory effects of hesperidin, tenoxicam and enoxaparin on intrapleural adhesions in an experimental rat model.

Methods: A total of 52 healthy adult male Wistar Albino rats from the same colony were randomly divided into six groups as sham (Group 1), surgical control (Group 2), low-dose hesperidin (Group 3), high-dose hesperidin (Group 4), tenoxicam (Group 5), and enoxaparin (Group 6). All subjects underwent left thoracotomy and except for the sham group, an adhesion model was applied and, postoperatively, the drugs were administered intraperitoneally. On Day 11 postoperatively, the rats were sacrificed and their blood levels of interleukin-1β and interleukin-10 were examined and they were evaluated for pleural adhesion area, adhesion severity score, mesothelial cell proliferation score, mononuclear cell infiltration score, and macrophage infiltration score in the collagen layer.

Results: The lowest adhesion area and adhesion severity score were found in Group 6. There was a statistically significant difference between Group 2 and Group 6 and between Group 3 and Group 6 in terms of both parameters (p=0.04 and p=0.02). As for adhesion area, a statistically significant difference was found between Group 5 and Group 6 (p=0.04). Statistically significant differences were also found between Group 2 and Group 5 in terms of mesothelial cell proliferation scores and between Group 1 and Group 4 in terms of mononuclear cell infiltration scores (p=0.03 and p=0.02).

Conclusion: Enoxaparin, tenoxicam, and high-dose hesperidin act at different points to prevent adhesion in rats.

Keywords: Experimental rat model, hesperidin, intrapleural adhesions, rethoracotomy.

ÖZ

Amaç: Bu çalışmada, deneysel sıçan modelinde intraplevral yapışkanlık üzerinde hesperidin, tenoksikam ve enoksaparininin antifibrinolitik ve antiinflamatuvar etkileri araştırıldı.

Çalışma planı: Aynı koloniden toplam 52 adet Wistar Albino cinsi sağlıklı erişkin erkek sıçan sham (Grup 1), cerrahi kontrol (Grup 2), düşük doz hesperidin (Grup 3), yüksek doz hesperidin (Grup 4), tenoksikam (Grup 5) ve enoksaparin grubu (Grup 6) olacak şekilde rastgele altı gruba ayrıldı. Tüm deneklere sol torakotomi yapılarak, sham grubu dışındakilere adezyon modeli uygulandı ve ameliyat sonrası ilaçlar intraperitoneal olarak uygulandı. Ameliyat sonrası 11. günde sıçanlar sakrifiye edilerek kanda interlökin-1β ve interlökin-10 düzeyleri incelendi ve plevral adezyon alanı, adezyon şiddet skoru, mezotel hücre proliferasyon skoru, kolajen tabakasındaki mononükleer hücre infiltrasyon skoru ve makrofaj infiltrasyon skoru açısından incelendi.

Bulgular: En düşük adezyon alanı ve adezyon şiddet skoru Grup 6'da tespit edildi. Her iki parametre açısından Grup 2 ile Grup 6 ve Grup 3 ile Grup 6 arasında istatistiksel olarak anlamlı farklılık saptandı (p=0.04 ve p=0.02). Adezyon alanı için de Grup 5 ile Grup 6 arasında istatistiksel olarak anlamlı farklılık saptandı (p=0.04). Mezotel hücre proliferasyon skoru açısından Grup 2 ve Grup 5 arasında ve mononükleer hücre infiltrasyon skoru açısından Grup 1 ve Grup 4 arasında istatistiksel olarak anlamlı farklılık saptandı (p=0.03 ve p=0.02).

Sonuç: Sıçanlarla enoksaparin, tenoksikam ve yüksek doz hesperidin adezyonu önlemek için farklı noktalarda etki göstermektedir.

Anahtar sözcükler: Deneysel sıçan modeli, hesperidin, intraplevral yapışıklık, retorakotomi.

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Surgical procedures can cause postoperative adhesions to varying degrees. When tissue damage occurs, tumor necrosis factors (TNFs) are released from macrophages, causing mesothelial damage, and inflammatory cells release type-1 plasminogen activator inhibitor (PAI-1). The PAI-1 increases adhesion formation by suppressing tissue plasminogen activator (t-PA) activity.[1] Typically, mesothelial cells prevent this fibrin deposition by producing t-PAs, converting plasminogen into plasmin and degrading fibrin. Although postoperative adhesion in the abdomen is undesirable, in thoracic surgery, it is desirable for the adhesion of pleural sheets, postoperative expansion of the lung to fill the thorax and the resolution of air leaks and pneumothorax, prevention of effusion, and hemodynamic stability. However, these adhesions are undesirable in cases requiring rethoracotomy due to the risk of serious complications.[1,2] Rethoracotomies can be performed due to various complications, such as bleeding, expansion defect, bronchopleural fistula, and foreign body in the pleural cavity. It is a method used in malignancy surgery (metachronous tumors, recurrent metastases), rarely in recurrent pneumothorax and, recently in patients with emphysema undergoing lung transplantation.[1-4] In this context, intraoperative dissection of adhesions between the hilum and/or the mediastinum and lung is more difficult.[5] Although experimental studies on the use of anti-adhesive biomaterials for thoracotomies have shown promising results, there are still many aspects that require further planning and investigation.[6,7]

In the present study, we aimed to investigate the concept of reducing possible intrapleural adhesions in patients undergoing rethoracotomy by systemically administering an easily available drug preoperatively instead of the previously-employed methods of using absorbable barriers.

MATERIALS AND METHODS

In this single-blind study, a total of 52 healthy adult male Wistar Albino rats weighing 250 to 300 g were used. The rats were individually caged at 55±5% humidity and temperature between 21°C and 23°C under a 12 h light-12 h dark cycle. The rats were randomly divided into six groups: Group 1 (sham; n=7), Group 2 (surgical control; n=9), Group 3 (low-dose hesperidin; n=9), Group 4 (high-dose hesperidin; n=9), Group 5 (tenoxicam; n=9), and Group 6 (enoxaparin; n=9). To perform the surgery, anesthesia was induced with ketamine (35 mg/kg intraperitoneal [IP]; Pfizer PFE Ilaçları A.Ş., Istanbul, Türkiye) and xylazine (5 mg/kg IP; Bayer Türk Kimya San. Ltd. Şti, Istanbul, Türkiye) and the surgical sites were shaved. The operation sites were disinfected with iodine solution in the lateral decubitus position. As a local anesthetic, 0.5 mg/kg of bupivacaine (Marcaine flacon®, 0.5%, 20 mL; Astra Zeneca Ilaç Sanayi ve Tic. Ltd. Şti, Istanbul, Türkiye) was injected subcutaneously and a thoracotomy of approximately 2 to 2.5 cm was performed through the left fourth or fifth intercostal space. No abrasion model was applied to the seven subjects in Group 1. Afterwards, they were checked for bleeding and air leakage and the ribs were approximated one by one with 3.0 prolene suture and the muscle and skin were closed with continuous sutures without using a drainage catheter for the thorax. Thoracotomy was performed on the same side and in the same way in the remaining subjects, nine in each group, and the parietal and visceral pleura above and below the thoracotomy incision were abraded with a dry 0.1-mL iodine tampon to prevent air leakage and bleeding, and an adhesion model was created; all rats were closed in a standard manner as in Group 1 (Figure 1). The rats were supplemented with 2 L/min oxygen, until the anesthesia wore off and spontaneous respiration was restored. Each group was kept in cages separately without postoperative antibiotics and each subject received two doses of 0.1 mg/kg intramuscular morphine HC (Osel İlaç Sanayi ve Tic. A.Ş., Istanbul, Türkiye) at 12 h intervals in the first 24 h. No IP medication was administered to Group 1 for the first 10 postoperative days. Group 2 received 1.5 mL/kg/day of dimethyl sulfoxide (DMSO; Merck KGaA, Darmstadt, Germany), as it is the solvent of hesperidin;[8] Group 3 received 50 mg/kg/day hesperidin (Sigma-Aldrich, Merck KGaA, Darmstadt Germany);[9] Group 4 received 100 mg/kg/day of hesperidin;[9] Group 5 received 0.5 mL/kg/day of tenoxicam (Mustafa Nevzat İlaç A.Ş, İstanbul, Türkiye);[10] Group 6 received 1 mg/kg/day-100 mg= 10,000 U-enoxaparin (Atabay Kimya Sanayi Ticaret A.Ş, İstanbul, Türkiye)[11] IP at the same time every day. While determining the low dose of hesperidin as 50 mg/kg/day and the high dose as 100 mg/kg/day, the studies of Guardia et al.[9] were utilized. Tenoxicam was administered as 0.5 mL/kg/day[10] and Enoxaparin was administered IP at the same time every day as 1 mg/kg-100 mg=10,000 U-/day as stated in previous publications.[11] Rats that developed infection (n=2 in Group 1 and n=1 in Group 5; n=3 rats in total) were excluded from the experimental protocol and the study was continued with 49 rats. In studies conducted by creating an adhesion model and placing a bioabsorbable material with the experimental animal,

Figure 1. Parenchymal damage by surgical procedure and creation of adhesion model.

durations ranged from one to three weeks in rat/mouse models. In this context, the rats were sacrificed using a lethal dose of ether on Day 11 after a 10-day study period,[1,6] as wound healing was complete and blood samples were collected for biochemical examinations. Subsequently, intrapleural adhesions were measured macroscopically by performing a rethoracotomy through the eighth or ninth intercostal space and the chest wall was removed *en bloc*, fixed in 10% formaldehyde and sent to the laboratory for microscopic examination (Figure 2, Table 1).[12,13]

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 24.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) or number and frequency. Analyses for conformity to normal distribution were performed; interleukin (IL)-1β and 10 parameters were assessed using the one-way analysis of variance test, since they showed normal distribution. Other parameters were analyzed using the Kruskal-Wallis analysis of variance. Post-hoc test, Tukey test, and Bonferroni-corrected Mann-Whitney U test were used. A p value of <0.05 was considered statistically significant.

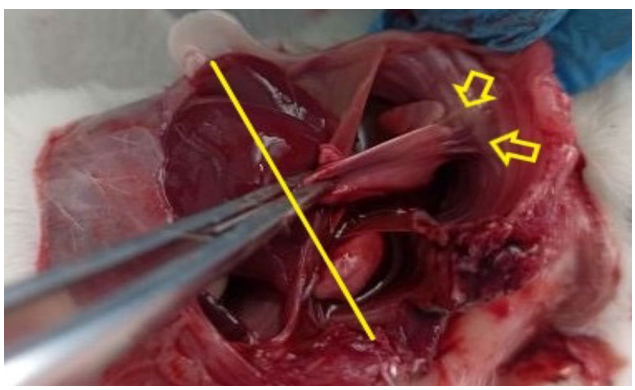

Figure 2. Macroscopic measurement of intrapleural adhesions by rethoracotomy and *en bloc* removal of the chest wall.

RESULTS

On macroscopic examination, the highest adhesion area (AA) and adhesion severity score (ASS) were observed in Group 2, while the lowest AA and ASS were observed in Group 6, followed by in Group 4. According to the intergroup comparisons, there was a statistically significant difference between Group 2 and Group 6 and between Group 3 and Group 6 in terms of both ASS and AA (p=0.04 and p=0.02), and between Group 5 and Group 6 only in terms of AA (p=0.04) (Table 2). In histopathological examinations, the highest and lowest mesothelial cell proliferation scores (MCPSs) were found in Group 5 and Group 2, respectively, where the difference was statistically significant (p=0.03) (Table 2 and Figure 3). There was a statistically significant difference between Group 1 and Group 4 in terms of mononuclear cell infiltration scores (MNCIS) (p=0.02) (Table 2 and Figure 3). The highest and lowest macrophage infiltration scores (MISs) were measured in Group 6 and in Group 3, but this difference was not statistically significant (p=0.41) (Table 2, Figure 3). The highest and lowest IL-1β in blood were measured in Group 2 and Group 5, respectively; the highest and lowest IL-10 were measured in Group 2 and in Group 6, respectively. In this context, no statistically

Table 1. Tabulation of the scales used for evaluation

Macroscopic examination (measured/performed)		Microscopic examination (with hematoxylin eosin (H&E) and immunohistochemical CD-68)			Blood
AA	ASS	MCPS	MNCIS	MIS	With ELISA
Area in front of the first thoracotomy incision (mm^2)	(1) no adhesion between the parietal pleura and the lung	(1) pleural surface completely covered with mesothelium	(1) presence of MNCI in the collagen layer-virtually absent/minor	(1) presence of macrophages in the collagen layer-virtually absent/minor	IL- 1β
	(2) removed by loose/blunt dissection	(2) 50% or more of the surface covered with mesothelium	(2) moderate/less than 100 MNCIs	(2) moderate/less than 100 macrophages	IL- 10
	(3) removed by moderate/some sharp dissection	(3) less than 50% of the pleural surface covered with mesothelium	(3) high/more than 100 MNCIs	(3) high/more than 100 macrophages	
	(4) severe/all removed by sharp dissection	(4) no mesothelial layer			

AA: Adhesion area; ASS: Adhesion severity score; MCPS: Mesothelial cell proliferation score; MNCIS: Mononuclear cell infiltration score; MIS: Macrophage infiltration score; ELISA: Enzyme-linked immunosorbent assay.

Table 2. Macroscopic, microscopic, and biochemically detected values of all groups

Values/groups	AA (mm^2)	ASS	MCPS	MNCIS	MIS	IL-1β	IL-10
Group 1							
Mean±SD	4.80±1.09	2±0.0	1.40±0.54	3.00±0.00	2.40±0.54	26.26±2.37	34.08±2.02
Median	4	2	1	3	2	26.40	33.40
Group 2							
Mean±SD	7.66±3.57*	2.55±0.88*	1.33±0.50*	2.11±0.60	1.88±0.78	27.43±2.67	37.05±5.23
Median	9	3	1	2	2	27.20	35.90
Group 3							
Mean±SD	7.66±4.18*	2.44±0.72*	2.11±1.05	2±0.70	1.77±0.44	26.77±3.48	36.77±5.63
Median	6	2	2	2	2	28.10	37.20
Group 4							
Mean±SD	5±4.18	1.88±0.92	2.11±1.05	2.11±0.33*	2.11±0.33	25.64±3.30	32.11±5.77
Median	4	2	3	2	2	25.20	30.10
Group 5							
Mean±SD	7.25±3.45*	2±0.53	2.62±0.74*	2.50±0.75	2.37±0.74	24.76±1.77	33.88±5.47
Median	9	2	3	3	2.5	24.20	34.65
Group 6							
Mean±SD	2.55±1.13*	1.33±0.50*	2.11±0.78	2.66±0.50	2.44±0.72	25.16±2.32	31.87±3.86
Median	2	1	2	3	3	25.20	29.70

AA: Adhesion area; ASS: Adhesion severity score; MCPS: Mesothelial cell proliferation score; MNCIS: Mononuclear cell infiltration score; MIS: Macrophage infiltration score; IL: Interleukin; SD: Standard deviation; * Significant *p* values are as follows ($p<0.05$); for AA Group 2-6: p=0.04, Group 3-6: p=0.01, Group 5-6: p=0.04; for ASS Group 2-6: p=0.04, Group 3-6: p=0.02; for MCPS Group 2-5: p=0.03; for MNC Group 1-4: p=0.02.

significant difference was found between the groups (p=0.19) (Table 2).

DISCUSSION

Intrapleural adhesion is frequently seen after surgical interventions for diseases involving the lung, trachea, esophagus, diaphragm, and mediastinum. Although this adhesion is often beneficial for thoracic surgery, adhesions that usually develop secondary to surgeries performed for metastatic or metachronous lung tumors, recurrent pneumothorax, and more rarely, emphysema, make the planning of a thoracic surgical procedure very difficult.[14] With advances in radiology and surgery, the need for secondary thoracic

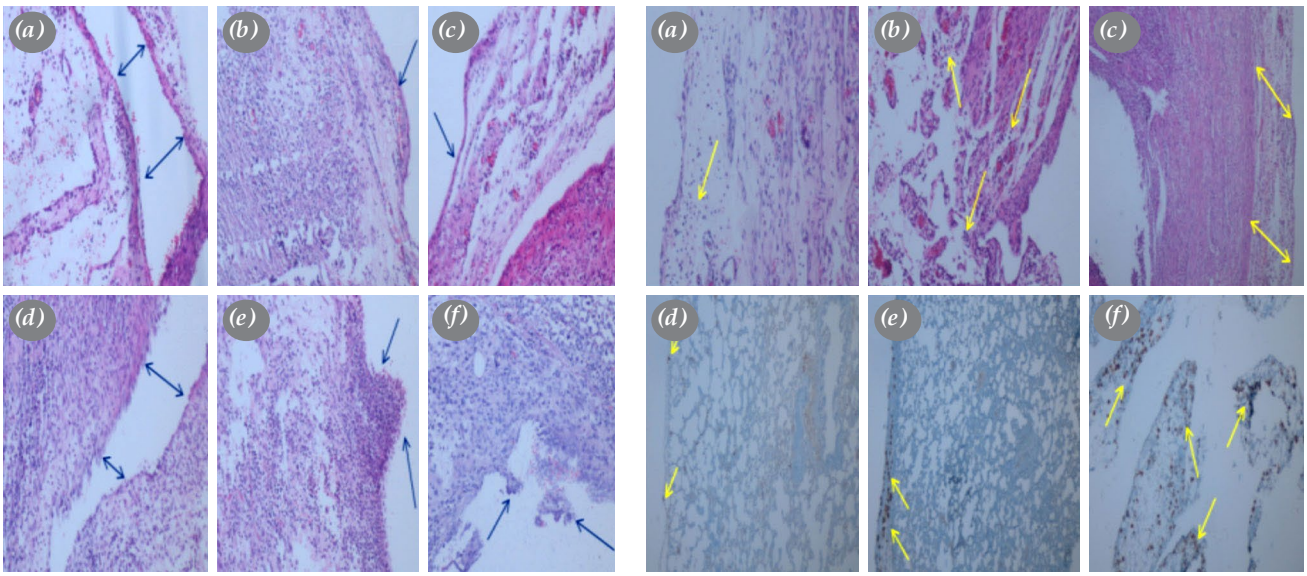

Figure 3. Left-pleural surface mesothelial cells (H&E, ×100); Right-hematoxylin eosin (H&E, ×100) and CD68 (×40) staining; **(a-c)** Inflammation (Grades 1-2-3, respectively) (H&E, ×100); **(d-f)** Brown staining of histiocytes by immunohistochemical CD 68 staining (Grades 1-2-3, respectively) × 40.

surgery has increased due to complementary surgical procedures and recurrent metastases, particularly in patients with malignancies, although it is very difficult to predict before the primary surgery whether a second surgery would be needed.[2] Recurrences after pulmonary metastasectomy occur in more than 50% of patients, making some patients potential candidates for repeat metastasectomy.[4] The benefits of repeat pulmonary metastasectomy for various primary tumor types and of repeat anatomical pulmonary resections for metachronous, ipsilateral, non-small cell lung cancer have been reported.[5,15] Considering that metastasectomy can be performed four times particularly for some specific types of metastases, rethoracotomy is expected in some patients.[16] However, rethoracotomy would increase intraoperative risk related to the surgical technique as there may be adhesions between the lung and the chest wall, mediastinum, and particularly the hilar structures (bronchus and/or pulmonary vessels).

Prevention of pleural adhesions studies, including our own study, were performed between the thoracic wall and the visceral pleura.[4,7,12] Different barrier studies, such as hyaluronate-based absorbable (HA) membrane, Interceed®, Seprafilm® and Prevadh® have been reported to effectively reduce both abdominal and intrathoracic postoperative adhesion.[12,17-20] Studies in rats with olive oil, garlic oil, argan oil, and honey which are among the organic substances mentioned in rumors from history, have also shown that postoperative intra-abdominal adhesion is reduced with these substances.[21] There is currently no substance routinely used to reduce intrapleural adhesion, as substances applied locally as barrier methods prevent adhesion only at the relevant surgical site.

In our study, we investigated the antifibrotic and anti-inflammatory effects of tenoxicam and enoxaparin, which are used in daily routine, and hesperidin, which has recently been frequently used in studies in different disciplines, on intrapleural adhesions to be formed in a rat experimental model. Tenoxicam was chosen, as it is an anti-inflammatory drug that is easily available in hospital pharmacies and used in daily routine. Ezberci et al.[10] showed that tenoxicam decreased postoperative intraabdominal adhesion in their study with 24 rats. Likewise, enoxaparin was also shown to reduce adhesions in a study by Türkçapar et al.[22] on LMWH application for the prevention of intraabdominal adhesions in 50 rats and heparin application was shown to reduce adhesions in the prevention of IP adhesions in rabbits by Fukasawa et al.[23]

Flavonoids, of which hesperidin is a member, have antioxidant properties such as elimination of different radicals, iron and copper chelation, alpha tocopherol regeneration, anti-tumoral, antiviral, antibacterial, antithrombotic, anti-inflammatory, antiallergic, antidiabetic, vasodilator and

immunostimulant properties. Hesperidin was reported to have anti-inflammatory and antioxidant effects in Kahraman et al.'s[24] study, and inhibited both acute and chronic inflammation in another study by Guardia et al.[9] with 35 rats in which the anti-inflammatory effects of three flavonoid species were compared with hesperidin. In this context, we attempted to show whether higher or lower doses of hesperidin were more effective. Since the optimal working doses of the other components were determined in previous studies, we used their standard doses, but not different doses.

Studies on the genetics of adhesion have revealed that, in the genes that code for TGF-β, PAI-1, vascular endothelial growth factor (VEGF), interferon-gamma (INF-γ), matrix metalloproteinases (MMPs), and IL, there are some genetic mutations, single nucleotide polymorphisms, and messenger ribonucleic acid (mRNA) mechanisms that increase the tendency for postoperative adhesion. It has been reported that more substances that are significant in the adhesion cascade at the injury site in cases of profibrotic or fibrotic diseases should be investigated genetically in future studies, so that patients at a higher risk for developing adhesion are identified in advance and recombinant therapies to prevent postoperative adhesions are developed for them.[25]

Rats have different characteristics from humans. According to the referenced studies, there is no drainage catheter in rat experimental models that require follow-up for a while, both as rats would not have any drainage catheter due to their rodent nature and as their recovery time is fast. Therefore, we did not use a drainage catheter in accordance with our experimental model. The lung expansion of rats followed without catheter placement is accepted to be complete in the studies we refer to. This situation can be explained as follows: rats have two lungs like humans, but the lungs are in a single hemithorax. Therefore, there should be no life-threatening pneumothorax. Since rats would not keep a drainage catheter on them, we set up a special device for our surgical experiment. We gave the rats continuous oxygen during the operation with this device and tried to aspirate the air inside as much as possible with specially prepared aspirators while closing the thorax after thoracotomy. Since the metabolism of rats is fast, they tolerate minimal pneumothorax. In our experiment, three rats could not tolerate this and exited and were excluded from the experiment.[1,12] Looking toward the future with a roadmap, it is vital to understand the pathophysiology of adhesion formation during the wound healing process; the *in vivo* degradation kinetics of materials; and the interaction of immune cells, mesothelial cells, and fibroblasts with the cells in damaged tissues. The fact that postoperative intrapleural adhesion studies in thoracic surgery are usually performed with a barrier method, almost never using systemic drugs led us to conduct this study. Our aim in planning this study was to find an inexpensive and easily applicable drug that would reduce possible intrapleural adhesions in any thoracic area, including the hilar region, in patients undergoing rethoracotomy. Thus, we sought to minimize the intraoperative risks for both the patient and the thoracic surgeon. According to the results of our study, enoxaparin increased MNCIS MIS and controlled inflammation; the anti-inflammatory effect of hesperidin, particularly at high doses, was close to that of enoxaparin. By its nature, tenoxicam, which is a non-steroidal anti-inflammatory drug (NSAID), minimizes the release of IL-1β, a proinflammatory cytokine, by suppressing the inflammation cascades and similarly inhibits the proliferation of the mesothelial cell layer that was damaged in response to inflammation, which is why it has the highest proliferation score. In summary, we observed that enoxaparin made a difference in postoperative macroscopic values and tenoxicam and high dose hesperidin made a difference in histopathologic examinations in terms of preventing adhesion. In thoracic surgery, we believe that further studies with larger animal populations and controlled human trials should be performed before recommending the use of drugs that can be given preoperatively to prevent adhesion, both in patients in the particularly at-risk group where tight adhesions are expected preoperatively and in those patients who require rethoracotomy.

The limitations of this study include the lack of a comparative double-dose study of low-dose hesperidine and the search for general anti-inflammatory biomarkers in the blood.

In conclusion, intrathoracic adhesions are expected more frequently after previous infections and thoracic interventions, particularly in patients in Türkiye. In future studies, patients who are at higher risk for preoperative adhesion development can be identified by investigating them in advance. In this context, many studies should be carried out to administer easy-to-use, low-cost drugs that reduce and/or eliminate adhesions to these patients.

Ethics Committee Approval: The study protocol was approved by the Necmettin Erbakan University KONÜDAM Experimental Medicine Application and Research Center Ethics Committee (date: 21.04.2020, no: 2020-024). Guidelines for Biomedical Research with Animals - ICLAS ethical rules were followed during our study.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to the article.

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