World Journal of Surgery and Surgical Research

Research Article
Published: 24 May, 2024

The Effect of Simvastatin on Complications Regarding Intraperitoneal Mesh Placement in Potential Septic Environment: Experimental Study in the Rat

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Abstract

Background: Hernia repair with the placement of an intraperitoneal mesh, especially in a septic or potentially septic environment, represents a relatively dangerous situation for postoperative complications. The present experimental study aimed to investigate the effect of simvastatin on the complications of a hernia repair with an intraperitoneal mesh in a potentially septic environment.

Materials and Methods: Three groups of 20 Wistar rats were categorized into groups A, B, and C. All rats underwent laparotomy and ciprofloxacin was administered. In groups B and C an enterectomy was performed, while in group C simvastatin was also administered intraperitoneally at a dose of 0.57 mg/kg. After the animals were sacrificed on day 21st, adhesion formation was recorded while a part of the mesh was sent for cultivation. The degree of neovascularization, inflammatory reaction, and fibrosis were also histologically evaluated. Blood samples were taken on the 7th, 14th, and 21st postoperative days to assess the following inflammatory markers: TNFα, IL-1α, and IL-6.

Results: In group C, the presence of significantly fewer adhesions as well as better histological results were reported compared to group B ($p<0.001$). In addition, similar results were found between group C and the control group. IL-1a, IL-6 and TNF-a were found significantly lower in the simvastatin group ($p<0.001$).

Conclusion: Intraperitoneal administration of simvastatin provided results almost identical to mesh placement in a clean environment. Being an easily accessible drug, we believe that it could become a new agent that will help us minimize the postoperative complications after intraperitoneal mesh placement.

Keywords: Simvastatin; Adhesion; Inflammation; Surgical mesh; Surgical Site; Infection

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Received Date: *30 Apr 2024*
Accepted Date: *16 May 2024*
Published Date: *24 May 2024*

Citation:
Kyziridis D, Mantzoros I, Parpoudi S, Makrantonakis A, Zapsalis K, Gemousakakis G, et al. The Effect of Simvastatin on Complications Regarding Intraperitoneal Mesh Placement in Potential Septic Environment: Experimental Study in the Rat. World J Surg Surgical Res. 2024; 7: 1549.

Abbreviations

LDL: Low-Density Lipoprotein; Surgical Site Infection (SSI)

Introduction

Hernias and incisional hernias constitute an everyday problem that every surgeon needs to face [1,2]. Over 22% of patients that undergo laparotomy present with incisional hernia within the first 3 years [1].

Simple hiatus suturing is associated with high relapse rates [3,4], so mesh placement has been the cornerstone of hernia repair over the last decades. Mesh replacement provides the best results with respect to postsurgical recovery, relapse rates, and post-surgical infection rates. Despite the fact that mesh placement provides numerous advantages, it is also associated with several adverse effects, such as higher Surgical Site Infection (SSI) rates, adhesion formation, and fistulas and seromas formation [5]. The vast majority of these adverse effects were associated with the inflammatory process that the presence of mesh establishes [6]. The most feared adverse effect is the infection of the mesh itself, and in this circumstance, the excision of the mesh may be necessary [7]. For this reason, several modern methods have been shot in order to prevent these adverse effects.

Statins are a group of medications that are broadly used to lower the level of Low-Density

Lipoprotein (LDL) cholesterol in the bloodstream. They have been proven not only to reduce the rate of atherosclerotic and cardiovascular events but also to reduce the overall mortality of patients at risk for cardiovascular disease [8]. Their pharmacologic action mainly regards the inhibition of HMG-CoA reductase, an enzyme that converts HMG-CoA into mevalonic acid. Mevalonic acid is a precursor substance that regulates the biosynthesis of cholesterol. In recent years, statins have been studied in detail and they are proven to provide multimodal action beyond their hypolipidemic effects. Many surveys have proven their anti-inflammatory action. The mechanism of action is not fully understood but it includes the inhibition of NF-κB, TNF-a, and IL-1b, which take part in the inflammatory response process [9]. Furthermore, statins show an antioxidant effect by inhibiting Rac1 and ROS. Lastly, statins can produce an antibiotic and anti-adhesion effect. They have been proven to have antibiotic action against numerous gram-positive and gram-negative pathogens, by inhibiting several biosynthetic pathways on bacteria and by inhibiting the action of biofilm at bacteria such as MRSA [10]. One possible mechanism of action of simvastatin for the prevention of intrabdominal adhesions is the increased level of tissue Plasminogen Activator (t-PA) and the decreased level of Plasminogen Activator Inhibitor-1 (PAI-1). This increase in the ratio is believed to accelerate the process of fibrinolysis and reduce adhesions [11].

The purpose of this study was to assess the effects of simvastatin on the complications of a hernia repair with an intraperitoneal mesh in a septic environment by histopathological evaluation, TNF-a l, IL-1a, and IL-6 blood count. To the best of our knowledge, after reviewing PubMed, this is the first-time simvastatin has been evaluated in an animal model of hernia repair in a septic environment.

Material and Methods

The study type refers to a randomized prospective experimental study in mice. The separation of the experimental animals was done randomly into a control group (witnesses) and intervention groups. The research is an experimental trial, namely a randomized, prospective, double-blind study, in which the comparison is made with a negative (placebo) control group. Experimental animals were procured from the Hellenic Pasteur Institute.

The use of animals in this study was in accordance with the ethical code approbated by the National Committee and obtained approval for conducting the research by the Greek Veterinary Services (reference number 23962/121).

Animals

Male Wistar strain rats were used as animal models in the study. A total of 60 mice aged 10 to 14 weeks and weighing between 200 and 300 g were used. Throughout the study, they were housed in specially designed cages (maximum of 2 mice per cage) at a temperature of 18°C to 22°C, relative humidity of 55% to 65%, and a light-dark cycle of 12 h light - 12 h darkness. The experimental animals were isolated from possible sources of noise and had free access to water and food (ad libitum). The animals were monitored daily, and the cages were cleaned twice weekly.

Design

The animal models were divided into three equal groups using electronic randomization software. In all groups, an intraperitoneal mesh was placed. The groups were designed as follows:

Group A: 20 animal models. Placement of a 2 cm × 2 cm intraperitoneal mesh, secured with 4 individual stitches using Prolene® 4/0, and intraperitoneal administration of 1 ml ciprofloxacin (2 mg/ml) and 0.2 ml 0.9% normal saline. Closure of the abdominal wall of the mouse was performed with 4 individual Silk 3/0 stitches in one layer. Blood samples were taken on the 7th, 14th, and 21st postoperative days, and the animal was sacrificed on the 21st day.

Group B: 20 animal models. Wedge resection of a segment of the colon 5 cm peripheral to the cecum and end-to-end anastomosis with 6 to 8 individual seromuscular stitches using Prolene® 5/0, after initially placing two guiding sutures on the mesenteric and anti-mesenteric lips, respectively. Placement of a 2 cm × 2 cm intraperitoneal mesh, secured with 4 individuals Prolene® 4/0 stitches, and intraperitoneal administration of 1 ml ciprofloxacin (2 mg/ml) and 0.2 ml 0.9% normal saline. Closure of the abdominal wall of the mouse was performed with 4 individual Silk 3/0 stitches in one layer. Blood samples were taken on the 7th, 14th, and 21st postoperative days, and the animal was sacrificed on the 21st day.

Group C: 20 animal models. Wedge resection of a segment of the colon 5 cm peripheral to the cecum and end-to-end anastomosis with 6 to 8 individual seromuscular stitches using Prolene® 5/0, after initially placing two guiding sutures on the mesenteric and anti-mesenteric lips, respectively. Placement of a 2 cm × 2 cm intraperitoneal mesh, secured with 4 individuals Prolene® 4/0 stitches, and intraperitoneal administration of simvastatin at a concentration of 0.57 mg/kg and 1 ml ciprofloxacin (2 mg/ml). Closure of the abdominal wall of the mouse was performed with 4 individual Silk 3/0 stitches in one layer. Blood samples were taken on the 7th, 14th, and 21st postoperative days, and the animal was sacrificed on the 21st day.

Access to the peritoneal cavity was achieved through a midline abdominal incision measuring 3 cm in length. The abdominal wall was carefully lifted, and on its peritoneal surface, a section of mesh measuring 2 cm × 2 cm was anchored with 4 individual sutures made of Prolene® 4/0. The mesh used was Ethicon Proceed®, which consists of a lightweight mesh made of polypropylene, polydioxanone, and polyglycolic acid.

In groups B and C, an additional wedge resection of a segment of the large intestine was performed, 5 cm away from the cecum. Subsequently, an end-to-end anastomosis was carried out using 6 to 8 individual seromuscular sutures with Prolene® 5/0, after initially placing two guiding sutures on the mesenteric and anti-mesenteric borders, respectively. In all groups, 1 ml of ciprofloxacin (2 mg/ml) was administered intraperitoneally, while in group C, simvastatin was also administered at a concentration of 0.57 mg/kg of body weight. Closure of the abdominal wall of the appendix was performed with 3 to 4 individual sutures using Silk 3/0 in a single layer.

Finally, the mice were euthanized on the 21st postoperative day during deep anesthesia with intracardiac injection of potassium chloride.

Laboratory evaluation

Blood samples were collected from the experimental animals on the 7th, 14th, and 21st postoperative day in order to assess the following inflammation markers: Tumor Necrosis Factor-alpha (TNF-α), Interleukin 1 alpha (IL-1α), and Interleukin 6 (IL-6). Their levels were measured using the ELISA method, following the manufacturer's instructions, by appropriately trained personnel (RAB0272, RAB0311, and RAB0479 kits, Sigma Aldrich, Merck). The coefficients of variation between measurements (inter-assay coefficient %) and

within measurements (intra-assay coefficient %) were <12% and <10% respectively. The minimum detectable quantities were 15 pg/ml for IL-1α, 30 pg/ml for IL-6, and 25 pg/ml for TNF-α.

Histology analysis

After the euthanasia of the experimental animals, a laparotomy was performed, and the extent of adhesions was evaluated. The adhesions were classified according to the Modified Diamond scale. Their extent was graded from 0 to 3, where 0 indicated the absence of adhesions, 1 indicated the presence of adhesions <25%, 2 indicated the presence of adhesions between 25% to 50%, and 3 indicated the presence of extensive adhesions >50%.

Additionally, a portion of the mesh was placed in a sterilized Eppendorf tube and sent for culture. Gram staining was performed, and any microorganisms present were identified. A second portion of the mesh was placed in a neutral 10% formalin solution and sent for histological examination to evaluate fibrosis and neovascularization (Table 1, 2). Paraffin sections, 2 μm thick, were examined under a microscope after hematoxylin and eosin staining.

Statistical analysis

For the statistical analysis of continuous variables, the modified ANOVA method with Bonferroni post hoc test was used, and the Kruskal-Walli's test was applied for group comparisons and different time points. Additionally, for comparisons between groups for categorical variables, Fisher's exact test and the Chi-square test were used. The continuous variables were analyzed within the framework of general linear models using the ANOVA method. The significance level was pre-set at $P \leq 0.05$ for all hypothesis testing procedures.

Results

A total of sixty experimental animals were included in the study. No deaths were recorded before the completion of the experiment, and all twenty animals from each group were analyzed at all predetermined time points.

Adhesions

According to the modified Diamond scale, the adhesions significantly increased in Group B (anastomosis and mesh placement) compared to Group A (control) (p<0.001), while they significantly decreased in Group C (anastomosis and mesh placement with simvastatin administration) compared to Group B (anastomosis and mesh placement) (p<0.001). However, there was no statistically significant difference in adhesions between Groups A and C (p=0.541) (Table 3).

Table 1: Classification of fibrosis.

Grade	Assessment of fibrosis according to histological examination
0	No fibrosis
1	Minimal, mild fibrosis
2	Moderate fibrosis
3	Severe, strong fibrosis

Table 2: Classification of neovascularization.

Grade	Assessment of neovascularization according to histological examination
0	No neovascularization
1	Mild neovascularization
2	Moderate neovascularization
3	Severe neovascularization

Table 3: Macroscopic and histological results.

	score	A	B	C	p
Adhesions	0	13 (65%)	0	11 (55%)	<0.001
	1	7 (35%)	1 (5.3%)	7 (35%)	
	2	0	12 (63.20%)	2 (10%)	
	3	0	6 (31.6%)	0	
Fibrosis	0	16 (80%)	4 (21.1%)	12 (60%)	<0.001
	1	4 (20%)	7 (36.8%)	8 (40%)	
	2	0	7 (36.8%)	0	
	3	0	1 (5.3%)	0	
Neovascularization	0	14 (70%)	2 (10.5%)	9 (45%)	<0.001
	1	6 (30%)	7 (36.8%)	10 (50%)	
	2	0	8 (42.1%)	1 (5%)	
	3	0	2 (10.5%)	0	

Table 4: IL-1a levels between the groups and the results of repeated measures ANOVA.

IL-1a	Week 1	Week 2	Week 3
Group A	0.333 ± 0.08	0.356 ± 0.11	0.356 ± 0.07
Group B	0.428 ± 0.09	0.431 ± 0.12	0.458 ± 0.10
Group C	0.305 ± 0.06	0.289 ± 0.08	0.305 ± 0.07
	[a,d]p<0.001, [b]p=0.002, [c]p=0.27		

Table 5: IL-6 between groups and results of repeated measures ANOVA.

IL-6	Week 1	Week 2	Week 3
Group A	0.333 ± 0.08	0.345 ± 0.1	0.381 ± 0.09
Group B	0.427 ± 0.1	0.431 ± 0.13	0.458 ± 0.11
Group C	0.301 ± 0.07	0.289 ± 0.09	0.34 ± 0.07
	[a]p=0.001, [b]p=0.002, [c]p=0.5, [d]p<0.001		

Table 6: TNF-a between groups and the results of repeated measures ANOVA.

TNF-a	Week 1	Week 2	Week 3
Group A	0.319 ± 0.1	0.358 ± 0.1	0.362 ± 0.05
Group B	0.392 ± 0.13	0.437 ± 0.1	0.43 ± 0.1
Group C	0.31 ± 0.06	0.323 ± 0.1	0.315 ± 0.1
	[a]p=0.001, [b]p=0.002, [c]p=0.2, [d]p<0.001		

Fibrosis

According to histological examination, fibrosis significantly increased in Group B (anastomosis and mesh placement) compared to Group A (control) (p<0.001), while it significantly decreased in Group C (anastomosis and mesh placement with simvastatin administration) compared to Group B (anastomosis and mesh placement) (p<0.001). However, there was no statistically significant difference in fibrosis between Groups A and C (p=0.409) (Table 3).

Neovascularization

According to histological examination, neovascularization significantly increased in Group B (anastomosis and mesh placement) compared to Group A (control) (p<0.001), while it significantly decreased in Group C (anastomosis and mesh placement with simvastatin administration) compared to Group B (anastomosis

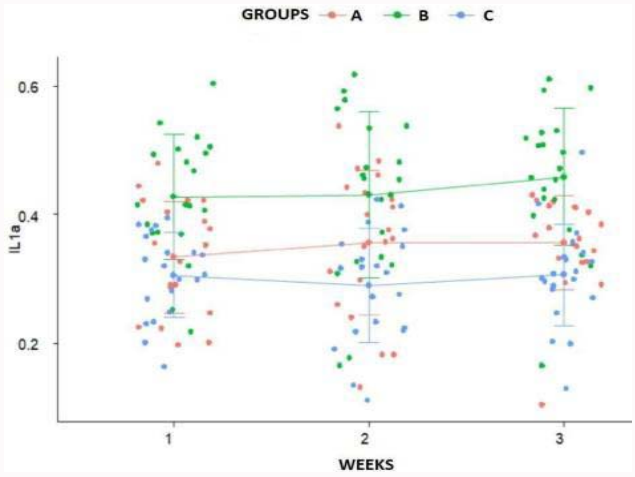

Figure 1: In this graph, it is evident that in Group B (anastomosis with mesh) in mesh placement in potentially septic environment the IL-1a levels show a significant increase in both mean values and distribution of various values across all three time points. The green line is considerably higher than the red line representing Group A (control). On the other hand, the administration of simvastatin significantly reduces IL-1a levels in terms of mean values and the distribution of various values across all three time points. The blue line is lower than both the red Group A (control) and the green Group B (mesh and anastomosis).

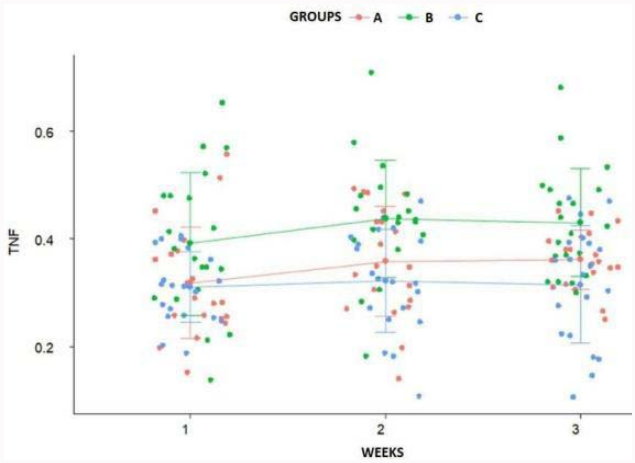

Figure 2: In this graph, it is evident that in Group B (anastomosis and mesh placement in potentially septic environment), the IL-6 levels show a significant increase in both mean values and distribution of various values across all three time points. The green line is considerably higher than the red line representing Group A (control). On the other hand, the administration of simvastatin significantly reduces IL-6 levels in terms of mean values and the distribution of various values across all three time points. The blue line is lower than both the red Group A (control) and the green Group B (mesh and anastomosis).

and mesh placement) (p<0.001). However, there was no statistically significant difference in neovascularization between Groups A and C (p=0.208) (Table 3).

Biochemical Markers

IL-1a: The statistical multivariate analysis using ANOVA showed a statistically significant difference among the groups (p<0.001) regarding IL-1a at all time points. Pairwise evaluation using Bonferroni post hoc test based on modified Kruskal-Wallis revealed a statistically significant increase in IL-1a in Group B (mesh placement) compared to Group A (control) at all time points (p=0.002). However, there was no statistically significant difference between Group A (control) and Group C (mesh placement with simvastatin) (p=0.27). Nevertheless, there was a statistically significant decrease in IL-1a from Group B (mesh implantation) to Group C (mesh implantation with simvastatin) (p<0.001) (Table 4, Figure 1).

IL-6: The statistical multivariate Analysis of Variance (ANOVA) showed a statistically significant difference among the groups (p=0.001) regarding IL-6 at all-time points. Pairwise comparisons using the Bonferroni post hoc test, modified qualitatively by Kruskal-Wallis, revealed a statistically significant increase in IL-6 in Group B (mesh placement) compared to Group A (control) at all time points (p=0.002). Conversely, there was no statistically significant difference between Groups A (control) and C (mesh placement with simvastatin) (p=0.5). However, there was a statistically significant decrease between Groups B and C (p<0.001) (Table 5 and Figure 2).

TNF-a: The statistical multivariate analysis using ANOVA showed a statistically significant difference among the groups (p=0.001) regarding TNF-a at all time points. Pairwise evaluation using Bonferroni post hoc test, based on modified qualitative Kruskal-Wallis, revealed a statistically significant increase in TNF-a levels in Group B (anastomosis with mesh) compared to Group A (control) at all time points (p=0.002). Conversely, there was no statistically significant difference between Groups A (control) and C (mesh implantation with simvastatin) (p=0.2). However, there was a statistically significant decrease between Groups B (anastomosis with mesh) and C (anastomosis with mesh and simvastatin) (p<0.001) (Table 6 and Figure 3).

Cultures

A large number of microbial groups were isolated from the culture of the sample in all groups. The heterogeneity of the isolated microorganisms does not allow for secure conclusions regarding the species and the mechanism of contamination. Indicatively, a higher percentage of *E. coli*, as well as other species of *Enterococci* and *Staphylococci*, were found. The statistical analysis was conducted

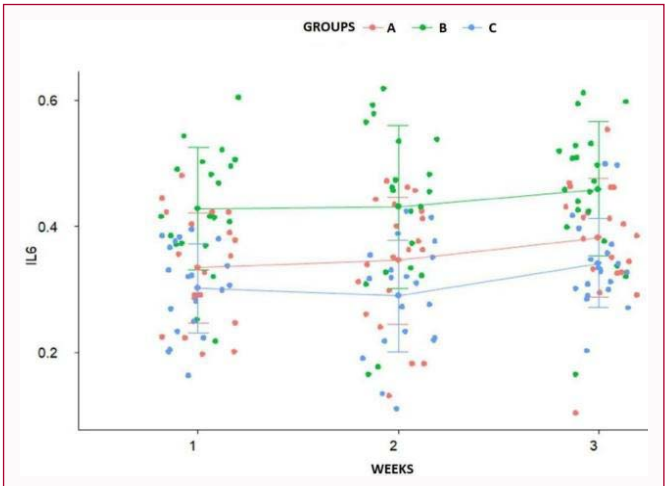

Figure 3: In this graph, it can be observed that in Group B (anastomosis and mesh placement in a potentially septic environment), the placement of mesh significantly increases TNF-a levels in terms of mean values and the distribution of various values across all three time points. The green line is much higher than the red line representing Group A (control). Conversely, the administration of simvastatin significantly reduces TNF-a levels in terms of mean values and the distribution of various values across all three time points. The blue line is lower than both the red Group A (control) and the green Group B (mesh and anastomosis).

Figure 4: Adhesions on Group B.

solely based on the positive cultures. The cultures differed significantly among all groups (p=0.001). Specifically, in Group B (mesh and anastomosis), the positive cultures were significantly higher compared to Group A (control) (p=0.001), while in Group C (mesh, anastomosis, and simvastatin), the positive cultures were significantly lower than in Group B (mesh and anastomosis) (Figure 4).

Discussion

In recent years, the use of mesh placement in a potentially septic environment has been considered safe by several researchers. In a recent systematic review by Maatouk et al., it was found that the use of mesh for hernia repair, even in potentially infected fields, is not associated with increased rates of postoperative infections compared to conventional suture closure of the abdominal wall [12]. On the other hand, Birolini et al. concluded that hernia repair using a synthetic mesh with simultaneous colorectal intervention is feasible without causing an increase in surgical site infection rates or mesh-related complications [13]. Moreover, Kurman et al. reported that the prophylactic use of an intraperitoneal mesh in patients with peritonitis significantly reduces the frequency of incisional hernia occurrence compared to simple suture closure of the abdominal wall [14]. As for surgical site infections and the formation of enterocutaneous fistulas, the results were approximately the same [14]. There are also several reports that even in cases of peritonitis or incarcerated hernia, the frequency of complications is not affected by the presence or absence of mesh [15,16].

However, several authors continue to argue that infection remains a contraindication for mesh placement, as in all the aforementioned studies, apart from wound infection, other factors such as the intensity of the intraperitoneal inflammatory response, the extent of intraperitoneal adhesions, or the presence of an abscess were not evaluated. In a study with 177 patients who underwent hernia repair with simultaneous enterectomy and mesh placement, Xourafas et al. reported a significant increase in infectious complications [17]. They also concluded that the use of drains, the size of the defect, and the type of enterectomy did not affect the occurrence of postoperative complications [17].

Complications accompanying mesh placement and the efforts to prevent them are directly related to the repair of postoperative hernias, where the use of meshes results in the mobilization of neutrophils, fibroblasts, and macrophages, as well as the final formation of collagen, thereby allowing inflammation to intervene in the normal integration of the mesh and leading to the occurrence of complications [18].

The purpose of this study was to investigate the anti-adhesive and anti-inflammatory action of simvastatin and its effect on complications from intraperitoneal mesh placement in a septic environment. In groups B and C, the enterectomy performed served as the factor leading to a potentially infectious environment. Intense mobilization of inflammatory cells was observed in the preparations of these groups, as well as a significant increase in inflammatory markers, without similar results in the control group.

Regarding the design of the experiment, the administration of simvastatin intraperitoneally was chosen as a one-time dose to have acceptable clinical application. The exact dosage of 0.57 mg/kg was determined based on data from past papers and decided as such to ensure sufficient concentration of the substance in the tissues and avoid toxicity levels. The study period after the intervention was set at 21 days in order to collect more data. This decision was made to avoid studying only the early adhesions since we know that during this time frame, the process of permanent adhesions is also activated. Additionally, in this phase, we can gather information about the development of dense adhesions through the study of active inflammation, which is a contributing factor to their formation. This persistent inflammation also affects the healing process, for which histological evaluation of fibrosis, inflammatory reaction, and neovascularization is necessary for monitoring and drawing conclusions.

Instead of a septic environment, the study was conducted under conditions of a potentially septic environment. Initially, this condition represents the most commonly encountered situation in clinical practice, and therefore, the study results would have a more direct relevance to the surgeon's everyday experience. Furthermore, in choosing the septic environment and the inoculation of bacteria in the rats, there was a risk of their death due to the septic condition itself, rather than our experimental intervention.

The presence of a septic or potentially septic environment, mimicking cases of patients with potential peritonitis, results in the release of inflammatory mediators and the formation of fibrinous exudate in the peritoneal cavity. This process promotes fibrosis and leads to the development of adhesions. The balance between deposition and degradation of fibrin plays a crucial role in this process through the activation of the fibrinolytic mechanism [19]. The mesothelial cells of the peritoneum appear to play the most significant role in regulating the fibrinolytic mechanism by producing tPA and PAI-1. It has been found that an increase in the tPA/PAI-1 ratio can accelerate the process of fibrinolysis, thereby preventing adhesion formation [11,20].

In a study by Haslinger et al., the effect of simvastatin was confirmed, as a significant increase in t-PA expression and a simultaneous significant decrease in PAI-1 expression were observed in human endothelial cells, regardless of whether cholesterol was reduced or not [21]. Regarding the intraperitoneal administration of simvastatin, experimental studies have been published confirming its anti-adhesive action. Javaherzadeh et al. found that local administration of simvastatin in intraperitoneal rats after laparotomy

was associated with reduced adhesion formation both clinically and histologically [22]. The same results were observed in the experimental model of Kucuk et al., who administered intraperitoneal simvastatin at a dose of 0.57 mg/kg [11].

The action of simvastatin on preventing adhesion formation was also evident from our results, as in Group C, where simvastatin was intraperitoneally administered, no significant difference in adhesion formation was observed compared to the control group. In contrast, in Group B, we observed pronounced adhesion development (grade 0 or 1 *vs.* 2 or 3 according to adhesion and neovascularization score).

Moreover, it has been found that simvastatin inhibits the activity of MMP-9, playing a significant role in limiting neovascularization and fibrosis [23]. This was also evident in our results, where apart from the reduction in adhesions, there was a decrease in fibrosis and neovascularization (grade 0 or 1 *vs.* 2 or 3 according to fibrosis and neovascularization score). Regarding oral administration, in a retrospective monocentric study involving 419 patients with postoperative adhesive ileus, it was found that the use of statins significantly reduced the need for re-intervention [24]. However, in a relatively recent randomized study involving patients undergoing colorectal surgery, no significant effect was reported on the activation of the fibrinolytic mechanism within the first 24 h postoperatively. Furthermore, from the analysis of clinical outcomes, no reduction in hospitalizations for adhesive ileus was observed in a 2-year follow-up after the surgery [25]. The effect of oral administration on the prevention of adhesion formation was also examined in the experimental model of Yild-iz et al., without any particular effect being observed [26].

In the study by Cakmak et al., simvastatin was administered to rats after enterectomy and anastomosis [27]. The euthanasia of the experimental animals took place on the 3rd and 7th day, and complications such as surgical site infections, intra-abdominal abscesses, strictures, and anastomotic leaks were recorded. Histopathological analysis showed that the administration of simvastatin resulted in improved healing of the anastomoses compared to re-epithelialization, reduced granulation tissue formation, decreased ischemic necrosis, and reduced inflammatory infiltration [27]. Although the aforementioned study had a relatively short duration, as the euthanasia of the rats was performed on the 3rd or 7th day, we observed similar histological results on the 21st day when the experimental animals were euthanized.

In 2016, Makay et al. published an attempt to investigate the effect of simvastatin on the prevention of adhesion formation after thyroidectomy. It was an experimental model conducted on rats and was the first to explore the impact of a factor on adhesion formation in neck reoperations. Two different doses of simvastatin were administered (0.5 mg/kg body weight and 0.8 mg/kg body weight). They found that even in the group that received a lower dose of the drug, significantly fewer to no adhesions were formed in the first and third month of the intervention, as well as a much lower degree of fibrosis [28].

Injury to the peritoneum triggers the initiation of the inflammatory process, accompanied by the release of cytokines such as Tumor Necrosis Factor-alpha (TNFa) and Interleukin-6 (IL-6), whose levels are directly associated with adhesion formation. This is followed by activation of coagulation, resulting in interactions between fibroblasts, fibroblasts, and angiogenesis. In our experiments, the increased extent of adhesions in Group B corresponded to elevated levels of inflammatory cytokines IL-1a, IL-6, and TNF-a, which are directly related to the response to the mesh and the induced peritonitis. A study by Yao et al. demonstrated the correlation between peritonitis induction and the production, by mesothelial cells of the peritoneum, of both inflammatory molecules such as TNF-a, IL-1β, and IL-6, and anti-inflammatory molecules such as IL-1RII and IL-10. The beneficial effect of simvastatin on inflammatory cytokines has been described by several authors [29-36]. In our experiments, the reduced levels of cytokines observed in Group C, where simvastatin was administered, corresponded to the histological findings of significant reduction in adhesions, fibrosis, and neovascularization.

In an experimental study conducted by Ciftci et al., investigating the effects of using a mesh in a septic environment, researchers observed a significant increase in adhesion formation, more pronounced fibrosis, and a higher mortality rate. The antibiotic used in this study was gentamicin, administered intramuscularly [34]. In previous studies ciprofloxacin was also used [36]. Similarly histological results were observed in our Group B, where only ciprofloxacin was administered. It was expected to have significant differences in the results compared to Group A, which represents a clean environment. What drew interest was the very good outcomes in Group C, where simvastatin was administered, potentially exerting a synergistic effect with ciprofloxacin.

In groups B and C, the trauma of enterectomy predisposes the development of pathogens on its own. From the results of the cultures, it was observed that group C had a lower percentage of positive cultures compared to group B, where only antibiotics were administered. Although not an antibiotic factor, it has been observed in many experimental studies that simvastatin possesses antimicrobial properties and can intervene in the cascade of inflammation and limit a septic condition. It acts by inhibiting multiple biosynthetic pathways and cellular processes in bacteria, including selective interference with bacterial protein synthesis, significantly reducing bacterial load and the mobilization of inflammatory cytokines [35,36]. Additionally, through its direct effect on extracellular polysaccharides, it reduces the formation and viability of the biofilm derived from *Staphylococcus aureus*, which consists of one or multiple microbial communities [10].

Conclusion

In conclusion, it was evident that simvastatin, through its anti-inflammatory, antioxidant, and antifibrotic actions, leads to a reduction in postoperative adhesions and decreases the inflammatory response of the body to foreign material. We also concluded that simvastatin does not interfere with the process of anastomotic healing, as we did not observe anastomotic leaks or intra-abdominal abscess formation. Therefore, we consider simvastatin to be a clinically useful factor without causing an increase in complications. However, the postoperative observation period in all studies, including our own, was not very long. Additionally, different doses of the drug were administered intraperitoneally in each study. Therefore, further and larger studies should be conducted to confirm these actions of simvastatin and to determine the optimal dosage for intraperitoneal administration.

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