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Original Article

The effect of atorvastatin topical solution on preventing peritoneal adhesion in rats

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Abstract

Background: Peritoneal adhesion is a critical postsurgical complication in abdominal and pelvic surgeries. Due to their anti-inflammatory and fibrinolytic properties, statins are assumed to reduce peritoneal adhesions effectively. Our study aimed to investigate the effects of atorvastatin topical solution on preventing postoperative peritoneal adhesion in rats.

Methods: Twenty male Wistar rats were used, and a 2–3 cm ventral midline incision was made under general anesthesia. The cecal abrasion model was used for the induction of peritoneal adhesion. Four groups of five rats were used: normal saline (negative control), hydrocortisone 1% (positive control), atorvastatin 1%, and atorvastatin 4%. All rats were sacrificed on the fifth postoperative day. The adhesions were scored as 1 to 4 microscopically and 0 to 5 macroscopically. A histopathological study was performed on the cecum and adherent bands. A blood sample was also taken for high-sensitivity C-reactive protein (hs-CRP) analysis on day 5.

Results: Histopathological evaluation showed that microscopic and macroscopic adhesion significantly decreased after using atorvastatin 4% compared to the normal saline group ($P=0.032$ and $P=0.008$, respectively). Atorvastatin 4% also significantly reduced the level of hs-CRP after abdominal surgery ($P=0.001$). The results with atorvastatin 1% were insignificant.

Conclusion: Atorvastatin 4% topical solution effectively prevented rat peritoneal adhesion, possibly through its anti-inflammatory effects. More extensive animal studies with atorvastatin and other statins and large human clinical trials are still needed to confirm the applicability and accuracy of the present findings.

Keywords: Atorvastatin, Peritoneal adhesion, hs-CRP, Abdominal surgery

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Introduction

Postoperative peritoneal adhesion after abdominal surgery is an important clinical and economic obstacle for the country's health care system. According to epidemiological studies, up to 95 percent of subjects develop adhesions following surgery, which increases the risk of long-term consequences such as small intestine obstruction, chronic pelvic pain, and infertility (1,2). Abdominal surgery and tissue manipulation, peritoneal ischemia, coagulation, infection, and release of inflammatory factors, including interleukins (ILs), vascular endothelial growth factor (VEGF), transforming growth factor β (TGF-β), and disruption in hemostasis are the most common causes of intraperitoneal adhesions (3).

Although many attempts have been made to prevent peritoneal adhesion with physical isolation or pharmacotherapy with anti-inflammatory agents, antibiotics, or fibrinolytics, none of these methods have been satisfyingly effective. On the other hand, some studies have shown that atorvastatin, which is an β-hydroxy β-methylglutaryl-CoA reductase inhibitor and is usually used to treat hypercholesterolemia, can reduce peritoneal adhesion following abdominal surgery (4,5).

One of the anticipated effects of statins in preventing peritoneal adhesions is their antithrombotic effect (6). Recent studies have revealed that atorvastatin decreases platelet activity and platelet-dependent thrombin production (PDTG), independent of LDL reduction

during the first week of treatment (7). Atalar et al have demonstrated that atorvastatin reduces the overall fibrinolytic capacity in the body after 12 weeks of intervention (8). Moreover, Bruni et al showed that atorvastatin can increase the fibrinolytic activity of the body (9). In addition, statins have demonstrated anti-inflammatory and antioxidant properties, which can prevent the occurrence of peritoneal adhesions after abdominal surgery (10-12). Haslinger et al showed that simvastatin is a strong activator of fibrinolytic activity in human mesothelial cells in normal and inflammatory conditions (13). Various inflammatory markers have been investigated to reveal the effects of statins on inflammatory disorders. For instance, high-sensitivity-C-reactive protein (hs-CRP) reflects low-grade systemic inflammation. Human research has demonstrated that statins can decrease serum hs-CRP levels in hyperlipidemic subjects (14). The level of IL-1β and TNF-α also decreases in hypercholesterolemic people treated with statins. This reveals that statins are effective not only in reducing vascular inflammation but also in reducing systemic inflammation (15).

It is assumed that statin use after abdominal surgery may reduce the incidence of intraperitoneal adhesions and their complications. Thus, this study investigated the impact of atorvastatin 1% and 4% topical solution in preventing peritoneal adhesion in rats with induced cecum abrasion. The intensity of macroscopic and microscopic peritoneal adhesion and hs-CRP serum concentration after peritonitis were used to measure atorvastatin's effect.

Methods

Drugs and chemicals

Atorvastatin calcium was purchased from Hakim® Pharmaceutical Co. The ethanol used in this study was obtained from Sigma®, USA. Ketamine was acquired from Alfasan®, Holland. Diazepam ampoule was provided by Caspian Tamin® Pharmaceutical Company. Other necessary materials were acquired from Sigma, USA. Hs-CRP 96 test kits were provided by Monobind® Company, United States. The injectable sodium chloride 0.9% serum (normal saline) was purchased from the Samen® Pharmaceutical Co. in Iran.

animals

Twenty male Wistar albino rats weighing 250 ± 25 g were purchased from the animal house of the Faculty of Pharmacy, Mashhad University of Medical Sciences, Iran. They were acclimatized and placed in standard cages in four groups. The animal enclosure exhibited adequate ventilation, maintaining a temperature range of 21 ± 2 °C, a humidity level of 60 ± 3%, and a 12-hour natural light and dark cycle. The rats had unrestricted access to regular water and food pellets used in laboratories. Spilled feed and rat feces were cleaned daily from the cage to provide good hygiene. All animals received compassionate treatment following the hospital's regulations. The experimental method was approved by the Ethics Committee of the Mashhad University of Medical Sciences (license number: IR.MUMS.MEDICAL.REC.1401.099).

Surgical technique

For anesthesia, the animals received ketamine/diazepam (100.5 mg/kg of body weight, intraperitoneally) (16). 1 mL of blood was obtained from the tail vein of the rats. The abdominal hair was removed, and the skin was disinfected using a 70% alcohol solution to perform the surgical procedure. Subsequently, an incision measuring 3 cm was created to obtain access to the abdominal cavity. The cecum was excised, and the pericecal region was gently abraded using a dry sterile gauze, resulting in a controlled induction of mild subserosal hemorrhage. A lavage was performed on the cecum area using 2 mL of normal saline, hydrocortisone 1%, atorvastatin 1%, or atorvastatin 4% sterile solutions. The abdominal skin and peritoneum were sutured using a non-absorbable 04 monofilament thread. Following the surgical procedure, the rats were confined to their respective enclosures within the designated recovery room. 1 mL of blood was drawn from the tail vein on the fifth day, and the serum was stored at minus 70 °C in a freezer. On the fifth day of the experiment, the rats were euthanized by administering ketamine and diazepam. Then, the rats underwent laparotomy, and samples of tissue from the cecum and peritoneum were collected and then sent for histopathological analysis and staining. The measurement of adhesion intensity was conducted using a scoring scheme for adhesion assessment.

The intervention groups

Twenty rats were divided into four groups of five: a negative control group, which only received sodium chloride 0.9%; a positive control group, which received hydrocortisone sodium succinate 1%; and two experimental groups, which received 1% and 4% W/V dosages of atorvastatin. A maximum of 0.5 mL/rat of normal saline was used as the solution's delivery system. On the fifth postoperative day, the rats were slaughtered using the laparoscopic method for further research.

Macroscopic evaluation

Macroscopic peritoneal adhesion was examined, graded, and blinded following the protocol described by Lauder et al (17). At the end of the study, all animals were sacrificed. The peritoneal adhesion and its shape were checked macroscopically. Under the guidance of an expert surgeon, each group received a score from 0 to 5 based on the thickness and number of adhesive layers, connecting surfaces, and presence of veins. Cecal and peritoneal lavage fluid samples were taken to evaluate the impact of atorvastatin therapy on inducible cytokines and oxidative

markers. The cecum and peritoneal lavage fluid was collected by flushing the same two mL of sodium chloride over the zone five times. The macroscopic adhesion score is divided into four scores according to inflammation, infiltration, and tissue fibrosis, as mentioned in Table 1.

Microscopic evaluation

After the animals were sacrificed and macroscopic evaluations performed, surgery was performed, and abdominal tissue samples were collected for pathological analysis. Hematoxylin and eosin staining were used to produce slides from the separated tissue samples. The pathologist analyzed the slides under a 100x magnification microscope (Olympus CX23) for signs of inflammation, fibrosis, infiltration of inflammatory cells, predominantly lymphomononuclear, and tissue necrosis.

Evaluation of inflammatory biomarkers

The concentration of hs-CRP, an inflammatory indicator, was determined in the peritoneal fluid of the samples on the fifth day using an hs-CRP kit (from Pariksha Biotech®, LOT number: P-hSCRP-3131), following the manufacturer's instructions.

Statistical analysis

Data are expressed as mean ± standard deviation (SD) and analyzed using one-way analysis of variance with Tukey's multiple comparisons post hoc test. Additionally, the frequency of peritoneal adhesion intensity on macroscopic examination was analyzed using the chi-square test and Dunn's multiple comparisons post hoc test. Statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA). P value < 0.05 was determined to be statistically significant.

Results

Macroscopic and microscopic comparison of intra-abdominal adhesion intensity between groups

Figures 1 and 2 represent the histologic and macroscopic findings of the tissue section prepared for different groups.

Figures 3 and 4 represent the microscopic and macroscopic comparison of intra-abdominal adhesion intensity between groups. The histological examination of the tissue samples in the hydrocortisone 1% group showed that the microscopic and macroscopic adhesion amount was significantly lower than in the normal saline group ($P = 0.005$). Notably, this group's microscopic and macroscopic adhesion was significantly lower than the group receiving atorvastatin 1% ($P = 0.016$ and $P = 0.032$, respectively). However, the comparison of adhesion between the group receiving atorvastatin 4% and hydrocortisone 1% showed that only the microscopic adhesion was significantly lower in the hydrocortisone group ($P = 0.032$), and macroscopic adhesion was not significantly different ($P = 0.095$).

The histopathological examination of the tissue samples in the atorvastatin 1% group also showed that the microscopic and macroscopic adhesion levels did not differ significantly from the normal saline group ($P = 0.690$ and $P = 0.310$, respectively).

Moreover, the histological examination of the tissue samples in the atorvastatin 4% group showed that the microscopic and macroscopic adhesion levels were significantly lower than the control group ($P = 0.032$ and $P = 0.008$, respectively).

Table 1. Microscopic and macroscopic adhesion score

Score	Microscopic	Macroscopic
0		No adhesion
1	Aggregation of fibrin and neutrophil infiltration	One thin adhesion
2	Edema, granulation formation, infiltration, and migration of connective tissue	More than one thin adhesion
3	Collagen formation	A thick adhesion with a deep connection
4	Fibrous formation	A thick adhesion with surface connections
5		Thick vascular veins inside the adhesion

Comparison of hs-CRP serum levels between groups

The serum hs-CRP level in the normal saline group was higher than in the other groups. The use of post hoc test and statistical analysis of the obtained values demonstrated that the level of hs-CRP in the hydrocortisone 1% and atorvastatin 4% groups were significantly lower than the normal saline group ($P < 0.001$ and $P = 0.001$, respectively). However, the mean hs-CRP levels in the atorvastatin 1% group were not significantly different from the normal saline group ($P = 0.45$). The difference between the hs-CRP levels in the group receiving hydrocortisone 1% and atorvastatin 4% was insignificant ($P = 0.125$). However, the level of hs-CRP in the hydrocortisone 1% group was significantly lower than the group receiving atorvastatin 1% solution ($P < 0.001$). Finally, the hs-CRP level in the atorvastatin 4% group was significantly lower than the atorvastatin 1% group ($P = 0.018$) (Figure 5).

Discussion

This study showed that the amount of microscopic adhesion after using atorvastatin 4% topical solution was significantly reduced compared with the normal saline group ($P = 0.032$). In addition, macroscopic adhesion decreased significantly after atorvastatin 4% administration compared with the normal saline group ($P = 0.008$). Atorvastatin 4% also significantly reduced the hs-CRP levels after abdominal surgery ($P = 0.001$). However, the use of atorvastatin 1% topical solution did not significantly prevent the occurrence of microscopic and macroscopic adhesions or reduce the hs-CRP levels

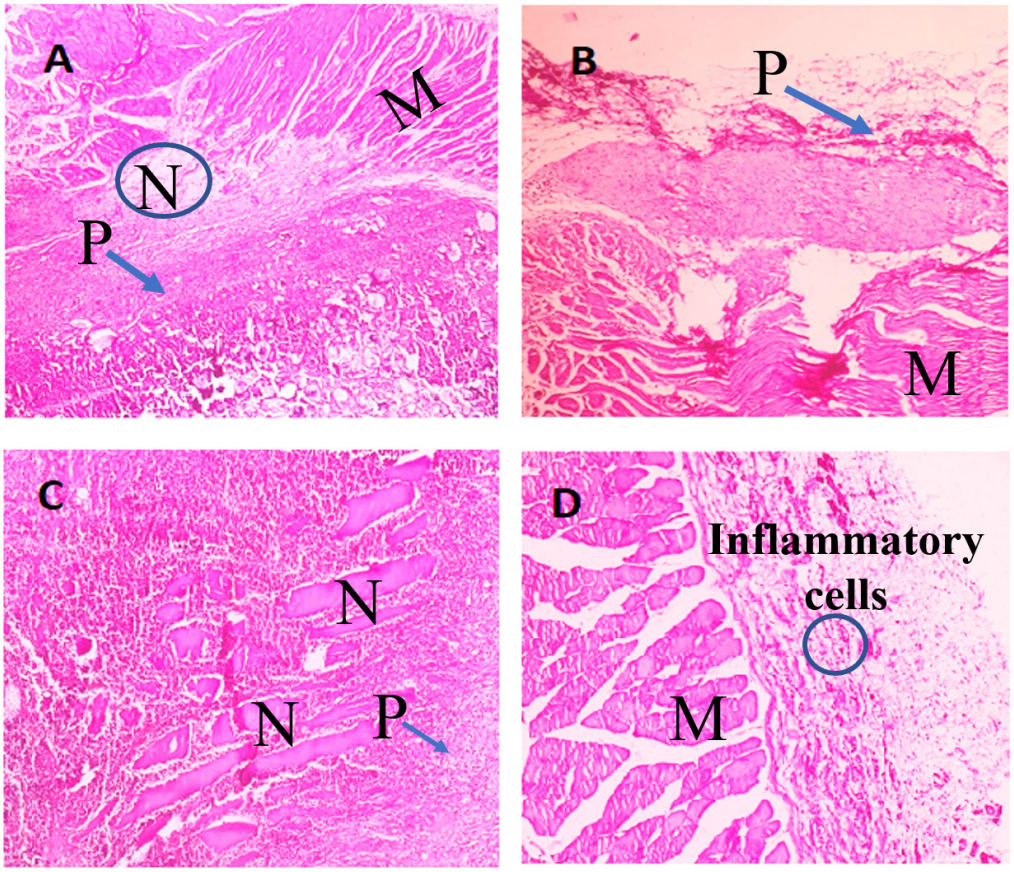

Figure 1. The histopathological changes of abdominal tissue in different groups of rats, stained with hematoxylin and eosin (×100 magnification). A) Normal Saline: vast necrosis, tissue destruction, and purulent inflammation can be seen in the lower half of the image, and muscle tissue is being destroyed in the upper half of the picture. B) Hydrocortisone 1%: germ tissue is observed in the small intestine and serosal layer of the peritoneum (the upper third of the picture) and the lower two-thirds of the picture of the muscular tissue of the abdominal wall. No cases were found in other parts of the tissue that are not visible in the picture. C) Atorvastatin 1%: acute purulent exudate is observed among completely necrotic striated muscle fibers. D) Atorvastatin 4%: mild inflammation exists in the serosal layer and on the right side of the striated muscular tissue of the wall, with a normal appearance. (M: muscle, N: necrosis, P: purulent inflammation)

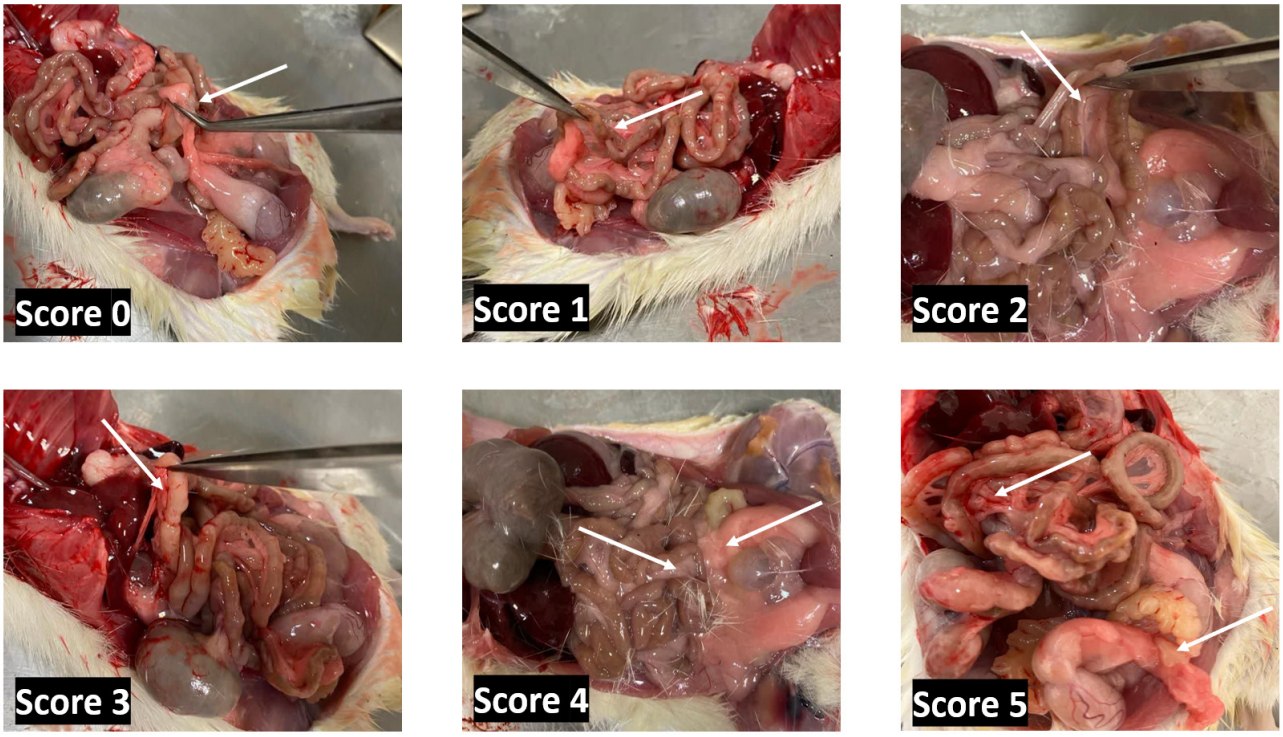

Figure 2. Macroscopic adhesion scores. Arrows indicate the site of adhesion

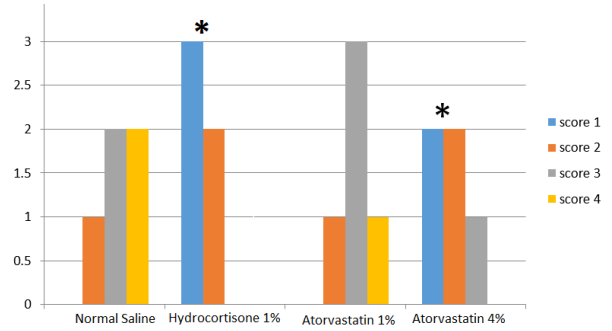

Figure 3. Microscopic comparison of intra-abdominal adhesion intensity between groups The microscopic intensity of adhesion in the groups receiving hydrocortisone 1% and atorvastatin 4% is lower than the control group ($P=0.005$ and $P=0.032$, respectively). *$P<0.001$

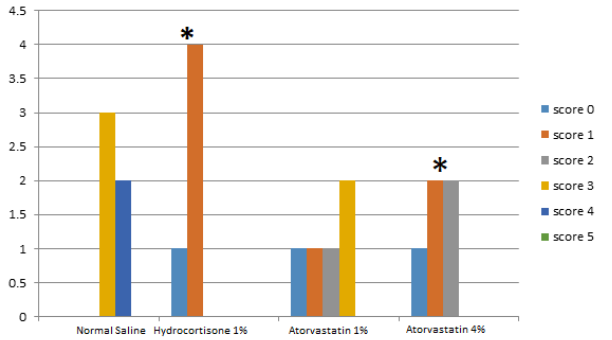

Figure 4. Macroscopic comparison of intra-abdominal adhesion intensity between groups The macroscopic intensity of adhesion in the groups receiving hydrocortisone 1% and atorvastatin 4% is lower than the control group ($P=0.005$ and $P=0.008$, respectively). *$P<0.001$

compared to the normal saline group.

The results of our research are compatible with previous findings. Several studies have demonstrated that statins effectively prevent postoperative adhesions when received intraperitoneally as a single treatment or in combination with mechanical barriers (18,19). Aarons et al. reported that statins effectively reduce intra-abdominal adhesion by creating a profibrinolytic state in the peritoneum without causing peritoneal bleeding (20). Their results suggest that statins reduce intra-abdominal adhesion via changing the peritoneal fibrinolytic state, mainly through the Rho/Rho kinase signaling pathway. Statins elevate the production of tissue plasminogen activator (tPA) and reduce the production of plasminogen activator inhibitor-1 (PAI-1) by human mesothelial cells. Increasing the ratio of tPA/PAI-1 increases the rate of fibrinolysis versus fibrinogenesis, resulting in less adhesion formation (21-23).

A study conducted by Lalountas et al in 2010 showed that intraperitoneal administration of atorvastatin before the completion of surgery significantly reduced the incidence of intraperitoneal adhesions in the studied rats. In their study, the use of atorvastatin had the same effect as hyaluronate/carboxymethylcellulose (as one of the standard methods used to decrease the occurrence of peritoneal adhesions); however, the implementation of hyaluronate/carboxymethylcellulose together with

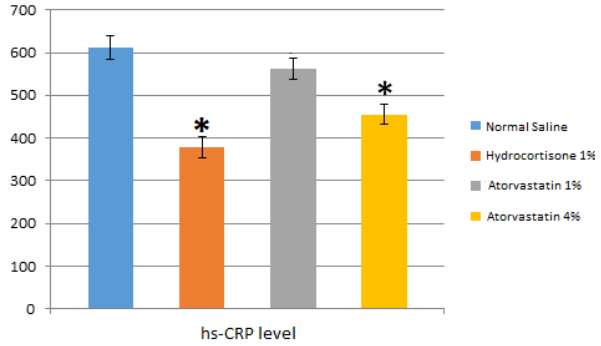

Figure 5. Comparison of serum hs-CRP levels (ng/mL) between groups. *$P<0.001$

atorvastatin caused a further reduction in adhesion (24). A systematic review and meta-analysis conducted on animal models showed that statins significantly reduce microscopic and macroscopic adhesions (25). Another large study conducted by Scott et al. on approximately one million patients in the USA and England showed that using statins during abdominal surgery significantly reduced the incidence of complications such as intestinal obstruction due to peritoneal adhesions (26).

In our study, using atorvastatin significantly reduced serum CRP levels, indicating the modulating effect of statins on acute inflammation after abdominal surgery. Interestingly, statins show their anti-adhesion effect when administered topically, but this effect is insignificant when administered orally. This is probably due to the partial metabolization of statins by the hepatic cells. Therefore, the concentration reaching the peritoneal cavity is insufficient for the expected effect (19). As a result, in our research, atorvastatin was used intraperitoneally. As statins are safe, inexpensive, and well-known drugs, their use might be feasible and effective.

Our study showed that using the cheap and low-risk drug atorvastatin can significantly reduce the occurrence of peritoneal adhesions following abdominal surgery. Therefore, using this medicine, we took a big step toward reducing complications after abdominal surgery. One of this study's strengths is that this drug's dose-dependent effectiveness has also been investigated by using two different concentrations of atorvastatin. However, among the cellular-molecular factors effective in creating peritoneal adhesions, only the level of hs-CRP has been examined. Several factors, such as VEGF, TGF-ß, and various types of ILs, influence the mechanism of peritoneal adhesions after abdominal surgery. Moreover, our study did not investigate the effectiveness of atorvastatin in combination with other medications.

Conclusion

In conclusion, using an atorvastatin 4% topical solution significantly reduced the number of microscopic and macroscopic adhesions in the rat peritoneum. In addition, serum hs-CRP levels were significantly reduced in rats

receiving atorvastatin 4%. The effects of atorvastatin 1% on adhesion and hs-CRP levels were insignificant. More extensive animal studies on atorvastatin and other statins and large human clinical research are still needed to confirm the applicability and accuracy of the present findings.

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Competing Interests
The authors declare no competing interests.

Ethical Approval
The Mashhad University of Medical Sciences Ethics Committee approved all the study procedures involving animals (IR.MUMS.MEDICAL.REC.1401.099).

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