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Original Article

Rosuvastatin's effects on ischemic skin flaps: Facts about statins' effects on skin flap viability

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Abstract

Aim: Statins are considered to be protective against ischemic injury because of their pleiotropic effects. In this animal study, the effects of high dose (40 mg/kg) rosuvastatin on ischemic skin flaps were investigated.

Materials and Methods: Eighteen Wistar Albino male rats randomly divided into the treatment and the sham groups in equal numbers (n=9 in each group). Orogastric tubes were used both in the treatment and the sham group. Differently, in our study orogastric feeding started one day before the surgery and ended on the postoperative day seven. By this way we aimed to have enough circulating levels of agent in acute ischemia. Only the treatment group received rosuvastatin-supplemented water. Twenty-four hours after the first gavage application, caudally based, modified McFarlane flaps were elevated in 3x10 cm in size. After flap elevation procedure, the flaps were returned to their original location immediately.

Results: The day after the last gavage application on postoperative day seven animals were sacrificed. Thereafter the digital images were obtained. The skin biopsies were taken by pathologist from three zones on each flap for histopathological assessment. Skin flap viability rate (p=0.508) and necrosis rate (p=0.453) did not show any difference between the groups Interestingly, the final weights of the animals were lower than their initial weights, but this was only significant for the study group (p=0.008), not for the sham group (p=0.400). There were no any expectations related with weight change of the animals before the statistical analysis.

Conclusion: On the other hand, there are literature studies claiming that the statins are effective to increase ischemic skin flaps viability, this study contradicts earlier studies. Statins were not observed to have favorable effects on critically ischemic skin flap viability through their pleiotropic activity.

Keywords: Ischemic skin; flap viability; pleiotropic effects; statins; weight loss

INTRODUCTION

Many preconditioning methods, such as sympatholytic, vasodilating, antithrombotic or anticoagulant agents, antioxidant substance use, and hyperbaric oxygen treatment, have been used to prevent necrosis in critically ischemic skin flaps to increase skin flap viability (1-3). However, among all these methods, surgical flap delaying is the only clinically practical method that has many times proven to increase flap viability (4-6). Increased morbidity, two-stage operations, and complication risk due to surgery are the significant disadvantages of surgical delaying. On the other hand, studies supporting the perfusion-enhancing and ischemia-inhibiting effects of cellular agents at the cellular level are available in the literature, and new agents are continuously tested in animal studies to observe these effects.

Rosuvastatin is a member of statins, which are 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors used to lower blood cholesterol levels in patients with high cholesterol levels. In addition, statins have other activities which are collectively known as pleiotropic effects (7), including anti-inflammatory (reduce c-reactive protein, adhesion molecules, and expression of cytokines, such as IL-1β, TNF α, IL-6 and IL-8), immunomodulating (reduce the expression of MHC II, TLR-4, and monocyte and macrophage proliferation, and blocking of T-cell activation via LFA-1 blockage), antithrombotic (reduce platelet activity and tPAI levels, increasing tissue plasminogen activator and thrombomodulin expression and activity), antioxidant (reduce NADPH oxidase and increasing Haem oxygenase), and lastly endothelial modulating (reduce iNOS expression and decreasing leukocyte adhesion) effects (8). The study aimed to investigate the pleiotropic

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effects of rosuvastatin on critically ischemic skin flaps by topographical measurements and histopathological assessment.

MATERIALS and METHODS

The study was conducted at The Experimental Medicine Research and Practice Unit after the approval of the ethics committee. Eighteen male Wistar Albino male rats weighing 238-370 gram (g) were equally divided into two groups (n=9 in each group) as treatment and control by the simple random sampling method. Mean weight of both groups was 307.77 g coincidentally. But mean standard deviation was 307.77 ± 44.43 for the treatment group and 307.77 ± 28.35 for the sham group. All rats were kept in separate cages under a 12-hour day-night cycle and fed with water and standard rat diet for eight days.

The rats were anesthetized by an intraperitoneal injection of 75 mg/kg ketamine HCL and 10 mg/kg xylazine HCL. The depth of anesthesia was followed by skeletal muscle tone and stimuli. The rats were shaved with a dorsal skin razor blade and then laid down and positioned on a fixed panel to pass the patches around the limbs (Figure 1A).

With the aid of a preformed 3x10 cm template, appropriate flap drawings were made on the back of the rats with the proximal part located between the bilateral iliac crests. The surgical site was cleaned with a povidone-iodine solution. After incision with a number 15 blade, a caudally based modified McFarlane flap was elevated with the panniculus carnosus left by the skin flap (9) (Figure 1B). Lastly, the flaps were returned to their original location and the incisions were sutured with 4.0 polypropylene sutures (Figure 1C).

Ambient temperature was fixed to prevent hypothermia. Each rat and its cage were labels. The animals were standardized with respect to environmental factors. The subjects were fed with a standard rat diet without water and diet restriction and kept at constant temperature and humidity.

Since the purpose of the study was to measure the effect of the agent on flap viability, the first rosuvastatin dose was given to the treatment group 24 hours before the surgery. Thus, the level of the agent was constant during and immediately after the surgery. Rosuvastatin was adjusted to 40 mg/kg in 2 cc of tap water as a single dose and orally administered to the rats via the orogastric catheter for eight days starting 24 hours before the surgery. The control group was given only 2 cc of tap water through an orogastric catheter.

The rats were sacrificed with intracardiac 100 mg/kg sodium pentothal one week after the surgery. Before the sacrifice, the whole dorsal skin tissue, including the flap, was removed entirely from the dorsal rat and transferred to containers filled with a 10% formaldehyde solution.

On the seventh postoperative day, the rats were photographed immediately after sacrifice on the same fixed plane on which they had been previously pictured. The position of the prepared plane for photography was always kept fixed and standard. Panasonic DMC-FZ50 was used to capture images. Then, the images were transferred to a computer using ImageJ 1.50i software to calculate the ratio of all non-viable and viable areas (Figure 1D).

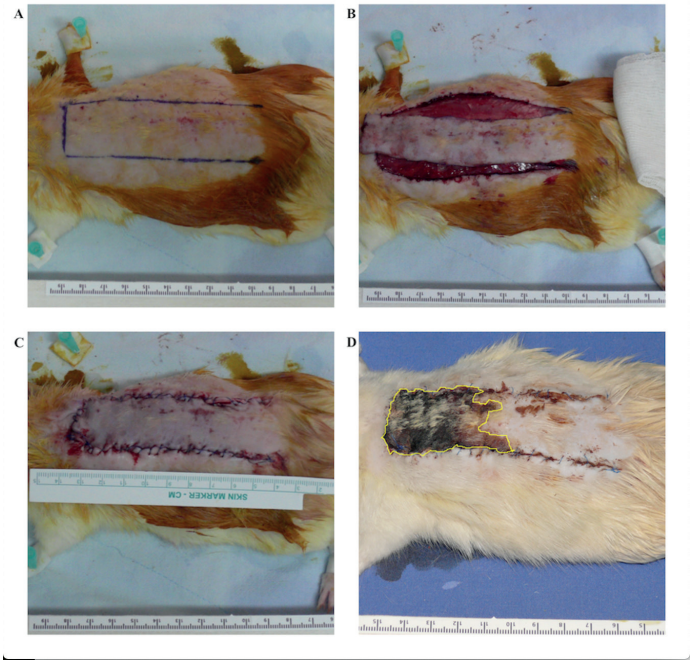

Figure 1. A: Preparation of rat dorsum for surgery by marking with aid of a template, B: Elevated rat dorsal skin flap, C: Completion of surgery by returning the flap to its position, D: Digital marking of the necrotic area on the rat dorsal skin flap after one week

The specimens were examined by the blind method. For histopathological analysis, three tissue samples from each flap were obtained from three areas: 2 cm from the caudal base (zone 1), 5 cm from the caudal base (zone 2), and 8 cm from the caudal base (zone 3). All the samples were fixed in 10% formaldehyde for 24 hours. The samples were embedded in the paraffin, and consecutively cut sections of 5 microns in thickness were examined.

The samples were stained with hematoxylin-eosin (H&E) and Masson's trichrome stain and evaluated for five parameters, namely the intensity of inflammation, neutrophil, necrosis, fibrosis, and vascular proliferation. These parameters were scored quantitatively as 0 for low and 5 for high tissue injury for histopathologic assessments under microscopy. The grading scale was developed by the pathologist according to normal tissue parameters. High inflammation, dense neutrophil infiltration, necrosis, fibrosis, and intense vascular proliferation resulted in a high total score. When the scores were calculated for each sample, a total tissue damage score of 0 to 25 was obtained. In the next step, the average of these scores for each group was estimated. The degree of ischemic injury was obtained based on the scores of the investigated parameters (Figure 2).

Statistical evaluation was performed using "IBM SPSS Statistics Version 22.0 for Mac" statistical program. The

Shapiro-Wilk test was used to determine whether the groups fit a normal distribution. Non-parametric tests were used for statistical analyses as groups did not follow a normal distribution. The Mann-Whitney U test was performed for the comparison of the groups. The Wilcoxon test was used for statistical analysis in dependent groups. The significance value was accepted as $p < 0.05$. The study was conducted at a 95% confidence interval (CI). The correlation between the variables was analyzed by the Spearman Rho test according to the analysis results of non-parametric tests. The mean ± standard deviation (SD) for the numerical data in the table was shown as the minimum and maximum values.

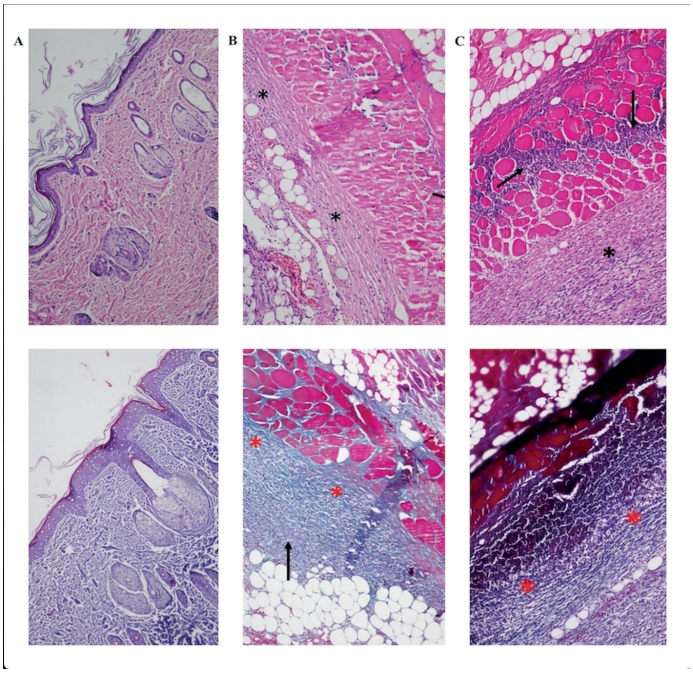

Figure 2. A: Post-staining image of Zone 1 with H&E staining (up) at 100x magnification and Masson's trichromic staining (below) showing limited fibrotic areas and inflammatory response, B: Post-staining image of Zone 2 with H&E staining (up) at 100x magnification and Masson's trichrome staining (below) showing PMNL infiltration and fibrosis in areas marked by arrows and stars, C: Post-staining image of Zone 3 with H&E staining (up) at 100x magnification and Masson's trichrome staining (below) revealing intensive PMNL infiltration and severe fibrosis in the areas marked by arrows and stars

RESULTS

At the end of the study, the flap viable area/total flap area measurement was 64.19± 7.19% for the study group, whereas it was 59.87±11.71% for the control group. Although the necrosis rates were lower in the study group, these differences were not statistically significant ($p = 0.453$). In the study group, the median total tissue damage score, which was the sum of the scores for zone 1, zone 2, and zone 3, was found to be 31.44 ± 8.45. Although this score was higher in the control group (33.88 ± 7.94), it was not statistically significant ($p = 0.626$).

The initial average weight measured as 307.7 ± 44.43 g for the treatment group and 307.7 ± 28.35 g for the control group, while the average weight immediately after the sacrifice was 289.3 ± 50.36 g for the treatment group and 306.2 ± 27.88 g for the control group. The difference between the initial and final weights in the treatment group was statistically significant as the final weight was significantly lower than the initial weight ($p = 0.008$). In the control group, there was no significant difference regarding the initial and final weights ($p = 0.400$) (Table 1).

A statistically significant positive correlation was found between the initial and final weights for all subjects (+0.941), according to Spearman's Rho test. This correlation was positively correlated (+0.917) for both the treatment group (+0.954) and the control group when examined separately. A statistically significant positive correlation (+0.474 and +0.501) was found between the baseline and final weight and necrotic area ratio when all subjects were evaluated together in a group-independent manner. Likewise, when all subjects were evaluated in a single group, there was a statistically significant negative correlation (-0.472 and -0.493) between the initial and final weight and the living/necrotic area ratio.

In brief, when the treatment group was compared to the control group, there was no statistically significant difference with regard to flap viability, and even ischemia parameters were lower in the former (Table 1).

Table 1. Comparison of statistical analyses and mean scores of histopathological parameters between the treatment and control groups

Parameters	Study (mean ± standard deviation)	Sham (mean ± standard deviation)	p
Initial Weight (gr)	307.77 ± 44.43	307.77 ± 28.35	0.4
Final Weight (gr)	289.33 ± 50.36	306.22 ± 27.88	0.008
Viable Area (cm^2)	13.85 ± 1.72	13.22 ± 2.94	0.402
Flap Area (cm^2)	21.69 ± 1.35	22.08 ± 2.08	0.354
Viable Area ratio (%)	64.19 ± 7.19	59.87 ± 11.71	0.508
Zone 1 Total Score	19.88 ± 4.59	21.66 ± 2.17	0.689
Zone 2 Total Score	8.55 ± 5.61	9.22 ± 5.76	0.592
Zone 3 Total Score	3.00 ± 0.86	3.00 ± 1	0.889
Inflammation	7.55 ± 1.81	7.77 ± 1.39	0.928
PMNL Infiltration	6.11 ± 2.36	6.22 ± 1.64	0.893
Necrosis	5.66 ± 2.50	6.55 ± 2.35	0.616
Fibrosis	6.77 ± 1.56	7.11 ± 1.83	0.748
Vascularity	5.33 ± 1.58	6.22 ± 2.86	0.498
Total Score	31.44 (± 8.45)	33.88 ± 7.94	0.626

DISCUSSION

Flap surgery is one of the essential parts of reconstructive surgery. Skin flaps are respectively simple than the other flap types because the donor site morbidity is low, the difficulties in closing the donor site are easily overcome (primary, secondary, or graft repair), no functional loss of the donor site is expected, and the complication rates are low. However, after elevation, the survival of the skin

flap is endangered due to ischemia (10). Since skin flap surgery is widely utilized, the contributions and signs of progress in this field are always welcomed.

Statins inhibit mevalonate synthesis in the liver, which is the rate-limiting step for cholesterol synthesis (11). Besides, statins have antithrombotic, antioxidant, and endothelial modulating functions. These additional properties of statins outside the liver are called pleiotropic effects (12-14), which are presumed to be protective against ischemic injury, and their efficacy is directly proportional to the dose.

Rosuvastatin is the most effective statin compared to the other statins at equal mg doses (atorvastatin, pravastatin, and simvastatin) and is also the most cost-effective statin (15-17). Comparing rosuvastatin to atorvastatin, Aydin et al. found that 20 mg/kg of rosuvastatin had the same efficacy as 80 mg/kg of a high dose of atorvastatin would produce in reducing hs-CRP, TNF and IL-6 levels among oxidative LDL and other inflammatory markers. Thus, they suggested rosuvastatin as an alternative to high-dose atorvastatin (18). In a study that compared the use of 10 mg/kg of atorvastatin, 10 mg/kg of pravastatin, 5 mg/kg of rosuvastatin, and 20 mg/kg of simvastatin on rats that had been exposed to cigarette smoking, it was reported that the best anti-inflammatory effect was seen in the rosuvastatin group while the simvastatin group had the highest antioxidant effect. However, when both oxidative stress and anti-inflammatory parameters were evaluated together, rosuvastatin was found to have the highest pleiotropic effect (19).

Jones et al. found an increase in the amount of eNOS after rosuvastatin administration, and this increase was attributed to the vascular protective effects (17). Liuni et al. demonstrated that rosuvastatin was an effective endothelial protectant against ischemia-reperfusion injury via COX-2 activation (20). Another prominent feature of that work was that it was the first direct drug-mediated endothelial preconditioning study. Similarly, Laufs et al. found that the positive effects of rosuvastatin on endothelium-mediated eNOS were independent of its lipid-lowering activity, and rosuvastatin was also effective against post-ischemic brain damage (21).

Pršíc et al. evaluated statins and anticoagulants regarding their efficacy in free flap surgery (22). They advocated the view that statins caused vasodilatation and inhibited microvascular thrombosis due to the increase in NO endothelium, which is mechanically and ischemically damaged in microcirculation caused by the correction of endothelial dysfunction. As a result, the authors suggested statin utilization for microsurgery. In another flap-related study, Karsenti et al. concluded that statins were beneficial in free flap surgery and attributed these beneficial effects to their pleiotropic properties (23). They also algorithmically recommended the use of atorvastatin at 40 mg/kg starting two weeks before free flap surgery.

To our knowledge, the relationship between statins and skin flap viability has been researched only in three animal study models. While simvastatin was used in a study carried out by Uygur et al., atorvastatin was evaluated by Chen et al. and Jia et al. (24-26).

Uygur et al. administered simvastatin intraperitoneally for seven days at a dose of 5 mg/kg. They concluded that statins positively contributed to the viability of the dorsal skin flap of rats. According to the authors, the possible reason for the contribution of statins was the increase in the expression of endothelial thrombomodulin (24). Chen et al. administered 10 mg/kg atorvastatin via an orogastric tube for one week. They observed improved viability on the survival of the dorsal skin flap of rats and attributed this to the ability of statins to enhance skin flap perfusion and vascular density through the VEGF-mediated pathway (25). Jia et al. also reported that 10 mg/kg of atorvastatin in diabetic rats improved the survival of the rat dorsal flap due to the increased capillary dynamics and efficacy of endothelial progenitor cells. But they did also find no benefit on the dorsal skin flap survival of non-diabetic rats (26).

On the other hand, rosuvastatin, which is the most potent statin, has not previously been investigated. Also, As mentioned above, the pleiotropic effects of statins are proportional to their dose. For that reason, in this study, we administered 40 mg/kg rosuvastatin, which is the upper limit for humans per day, and it is within the safe dose limits, according to Leiter (27). Because the studies conveyed by Uygur et al. and Chen et al. were one week, we also find enough and preferred a one-week period to convey our study (24,25). It is enough time period to see necrotic and other end results related to ischemia. But we made a small difference in relation to the other three studies. We applied the agent also one day before the surgery. We aimed with this to have enough agent amounts in circulating blood at the very minute of causing acute ischemia with surgical incisions. It is because not to miss the effects of agent also on the acute ischemia. This style, application of agent one day prior to surgery to have enough amount levels of agent in the circulating blood during surgery, is not a standard in animal studies chasing for the effects on flap viability. And we believe this a positive and novel aspect of our study design.

Because two of the three studies have utilized the gavage application of the agent, we also preferred this method for agent application. Our study was much more similar to the research that conveyed by Chen et al. (25). The significant differences from that study were the agent itself with its particular dosage and extra application of agent one day prior to surgery. On the other hand, the severity of ischemia can be measured by the levels of pro-inflammatory cytokines (TNF, IL-1, IL-6) gene expression or the histopathologic interpretation under the microscope (28). The first method may be more accurate, but the second method is also acceptable and easily applicable

at low cost as in our study. In another study these pro-inflammatory cytokines levels also might be utilized for more precise observation of ischemic end results.

In our study, investigating the effects of rosuvastatin on the rat dorsal skin flap viability, we did not observe any statistically significant difference between the groups. These were similar to non-diabetic rats of Jia et al. (26). Although the proportion of the viable area to the entire flap area was higher in the treatment group (64.19%) with respect to the control group (59.87%), the difference was not statistically significant (p = 0.508). Similarly, the mean score of the histological injury parameters was more negative in the control group with respect to the treatment group, but the difference between the mean scores of these parameters was also not statistically significant (p = 0.626).

When we compare our end result, which is the improved viability of the skin flap, with the other previous studies, we can tell that neither the delivery method of the agent nor the study period is not dependent variable for the end result. Because Uygur et al. and Chen et al. both studied their animals for one week (24,25). So, we can tell that the time period was also enough in our study. Again, in these studies for the first study, the delivery method was an intraperitoneal injection, and for the latter one, it was gavage application. Both studies have resulted in improved ischemic skin flap viability. Then we can tell that the delivery method also is not a dependent variable for the end result. In all of the three previous animal studies related to statins' pleiotropic effects on ischemic skin flap viability, each has measured the end result with different parameters (24-26). In the study that conveyed by Uygur et al. vascular endothelial thrombomodulin levels, in the study than conveyed by Chen et al. vascular endothelial growth factor (VEGF) mRNA expression levels and in the study that conveyed by Jia et al. endothelial progenitor cells have been measured at the microscopic level.

In our study, we only used classical histopathologic parameters to see if there was any relation of rosuvastatin and improved ischemic skin flap viability. But we did not find any statistically significant improved end result. And this circumstance was not only restricted to rosuvastatin. Besides our study, in the study that conveyed by Jia et al., they did find improved effects of atorvastatin (10/mg/kg/day) on the ischemic skin flaps of diabetic rats but no improved effect on the ischemic skin flap of non-diabetic rats (26). But this study also contrasts with the study that conveyed by Chen et al. in which they did also used atorvastatin (10/mg/kg/day) with the same method of delivery resulting with improved ischemic skin flap viability in non-diabetic rats (25). Ultimately, we can tell that statins' pleiotropic effects do not improve ischemic skin flap viability, as suggested by the previous animal studies. This brings in mind that pleiotropic effects of statins might be exaggerated or at least we can tell that for ischemic random skin flap viability.

The only statistically significant result in our study was between the weights of the treatment group before and after the research (p = 0.008). The rats in the treatment group had an initial average weight of 307.77 g and a final average weight of 289.33 g. However, this was not the case for the control group (p = 0.400), which had an average initial weight of 307.77g and a final average weight of 306.22 g. We are not aware of any literature that directly relates statins to weight loss, but there are two studies indicating that being on preoperative statin therapy is positively related to increased weight loss in post-bariatric surgery patients (29,30). But there is no randomized clinical trial investigating this effect.

Our findings indicate that rosuvastatin did not significantly yield an increase in the dorsal skin flap viability of the rats (Table 2). These contradict the results of the previous three studies that concluded improved skin flap viability after the utilization of a statin (24-26). Our study revealed that the most potent statin, rosuvastatin, was not protective against ischemic injury. This is supported by Heuvel et al., who conducted a clinical study with a group of patients that accepted statin intake (31). They demonstrated that the chronic use of statin failed to serve as a protective measure against ischemia-reperfusion injury. Similarly, Koolen et al. concluded that statins did not have an advantage in relation to ischemia-reperfusion complications in free flap breast surgery (32).

Table 2. Comparison of animal studies in the literature that utilized statins to reveal their relationship with flap viability

Study	Year	Agent	Dose	Administration	Flap Survival Effects	Weight Effects
Uygur et al (24)	2010	simvastatin	5mg/kg	intraperitoneal	via endothelial thrombomodulin	not available
Chen et al (25)	2013	atorvastatin	10 mg/kg	gavage	VEGF-mediated pathway	not available
Jia et al (26)	2017	atorvastatin	10 mg/kg	gavage	endothelial progenitor cells in diabetic group / no benefit in nondiabetic group	not available
Our Study	2020	rosuvastatin	40 mg/kg	gavage	no benefit	decreased weight

More importantly, in a randomized controlled clinical trial of Zheng et al. conducted with 1922 patients that underwent elective cardiac surgery, no difference was found between the rosuvastatin and placebo groups in means of reduced cardiac damage (33). However, there was a statistically significant increased risk for acute renal injury in the rosuvastatin group when compared with the placebo group. Hu et al. obtained similar results, suggesting that statins did not have a protective effect on myocardium during ischemia (34). As can be seen in the review of the literature, there are conflicting reports regarding the benefits of the pleiotropic effects of statins. As mentioned above, also Chen et al. also concluded that atorvastatin is not beneficial for ischemic skin flap survival in non-diabetic rats as we can conclude that statins' pleiotropic effects do not improve ischemic skin flaps of non-diabetic rats. So, we can tell that rosuvastatin does not have promising results like the agents (aspirin, heparin, dextran) that are believed to improve the effects of ischemia.

CONCLUSION

In contrast to previous animal studies claiming increased rat dorsal skin flap viability with the use of statins, we did not obtain similar results supporting this data. In our study model, rosuvastatin failed to increase skin flap viability. Another important finding in our study was that there was a statistically significant weight loss in the treatment group when compared to the control group. This raises an important question concerning whether statins have a weight loss effect and whether they could be used in that manner. To our knowledge, there are no studies examining statins with regard to their impact on weight decrease. Thus, further randomized controlled animal studies are necessary to examine this relationship carefully.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: Our study was carried out in Kocaeli University Experimental Medicine Research and Application Unit (KO-DETAB) after the approval of KO HADYEK ethics committee dated 20/10/2016 and numbered 6/3-2016.

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