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ORIGINAL ARTICLE

The Effects of Simvastatin on Ischemia Reperfusion Injury in an Experimental Colon Anastomosis Model

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Abstract Anastomotic leakage is more frequently reported in colonic anastomoses. Ischemia reperfusion injury is one of the main reasons for anastomotic leakage. Simvastatin is known to prevent tissue damage induced by free oxygen radicals after ischemia reperfusion injury. The effect of simvastatin on colonic anastomosis impaired by ischemia reperfusion injury is investigated. Single layer, end-to-end colocolic anastomosis after 0.5-cm colon resection was performed in Wistar Albino rats. In Group 1 (control) ($n = 10$), colonic anastomosis without I-R was performed. In Group 2 ($n = 10$), the superior mesenteric artery was clamped for 10 min followed by 60 min of reperfusion after which resection anastomosis was performed. In Group 3 ($n = 10$), 10 mg/kg simvastatin was given by gavage for 7 days after I-R and resection anastomosis. In Group 4 ($n = 10$), the rats received 10 mg/kg simvastatin by gavage 7 days before and 7 days after ischemia reperfusion and surgery. All of the rats were sacrificed 8 days after surgery. Anastomotic bursting pressure and tissue hydroxyproline levels were measured. Postoperative administration of simvastatin restored the anastomotic bursting pressure and hydroxyproline levels to that of control group thus overcoming the effect of ischemia reperfusion injury. Simvastatin administered postoperatively in an experimental model of colonic resection anastomosis impaired by ischemia reperfusion injury increased anastomotic bursting pressures and tissue hydroxyproline levels. Further experimental and clinical studies will show whether administration of simvastatin will increase reliability of the anastomosis and decrease postoperative morbidity and mortality in colonic anastomosis after ischemia reperfusion injury.

Keywords Superior mesenteric artery occlusion · Simvastatin · Colon · Anastomotic healing · Ischemia reperfusion · Rat

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Introduction

Anastomotic leakage is the most feared complication after colonic anastomosis occurring in nearly 15 % of patients. Among gastrointestinal anastomoses, colonic anastomoses are more prone to leak. Significant morbidity and sometimes mortality is inevitable if prompt diagnosis and appropriate treatment are not undertaken [1, 2].

The success of all anastomoses depends on several factors. Poor nutritional status of the patient, presence of anemia and chronic diseases like atherosclerosis, chronic renal failure, diabetes, and chronic pulmonary obstructive disease, and steroid administration increase the possibility of an anastomotic leak [3]. There are local factors that are traditionally regarded as a "must" when constructing the anastomosis. The anastomosis should have an adequate blood flow and should be constructed without tension. Signs of inflammation and infection should be absent or minimal in the peritoneum [2, 3]. The frequency of anastomotic leak increases when the anastomosis is accomplished in the more distal part of gastrointestinal tract. Matrix metalloproteinase activity and number of microorganisms are higher in colon and rectum [4, 5].

Adhering to surgical rules and choosing the right anastomotic technique for the best surgical outcome has long been a topic of debate and seems to continue. Nevertheless, an anastomosis with good blood flow and without tension, constructed with appropriate anastomotic technique, is the aim of all general surgeons [3].

Adequate blood flow is mandatory for optimal healing of an anastomosis. Ischemia, caused by the shortage of blood flow to the organ or tissue perfusion, results in reversible or irreversible cell and tissue damage [6]. After ischemia, free oxygen radicals (FOR) such as hydroxyl radical, peroxyl radical, hydroxyperoxyl radical, singlet oxygen, and superoxide anion are quickly produced upon the restoration of blood flow to the tissue (reperfusion) and the reintroduction of molecular oxygen to the cell [7–9]. Released in the reperfused bowel, FOR cause harmful effects such as impaired cellular functions and necrosis occurs in ischemia reperfusion (I-R) injuries [10].

Statins, known as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, are commonly used drugs for the coronary artery and hyperlipidemia patients, due to their cholesterol- and lipid-lowering effects. The use of statin is known to reduce mortality in atherosclerosis patients. Statins have antioxidant, anti-inflammatory, immunomodulatory, and endothelial dysfunction-correcting effects. They inhibit procoagulant activity and platelet functions [11].

In surgery, I-R injury may develop in cases such as major trauma, hemorrhagic shock, septic and hypovolemic shock, volvulus, mesenteric vascular diseases, necrotizing enterocolitis, inflammatory bowel diseases, and intestinal transplantation [10–12]. Anastomotic leaks are unfortunately common after I-R injuries.

Materials and Methods

The present study was approved by the Kırıkkale University Animal Experiments Local Ethics Committee (April 26 2012, #12/175). The study was then conducted at the Kırıkkale University Health Sciences Research and Application Center.

In this study, 40 Wistar albino rats, weighing 260–280 g, were used. The rats were taken into the laboratory 1 week prior to the study and fed with water and standard rat food and kept at 21 °C. The rats were divided into four equal ($n = 10$) groups. The resection anastomosis (R-A) procedure was performed by single layer, end-to-end colocolic anastomosis with 5/0 round-tipped polypropylene after 0.5-cm colon resection. The I-R procedure was performed by occluding the superior mesenteric artery (SMA) with an atraumatic clamp for 10 min to induce ischemia and by removing the clamps after color change to induce reperfusion for 60 min.

Anesthesia was induced by intraperitoneal ketamine 90 mg/kg (Ketalar, 500 mg/10 ml Pfizer; USA) and xylazine 10 mg/kg (Rompun, Bayer, Leverkusen, Germany) administration in all of the rats. After the abdominal regions of the rats were shaved and cleaned with povidone-iodine, a laparotomy was performed through a midline incision of about 3 cm under sterile conditions.

Group 1: R-A was performed without I-R. Group 2: R-A was performed after I-R. Group 3: R-A was performed after I-R. Simvastatin (Zocor 10 mg tablet, Merck Sharp and Dohme Drugs, Turkey) 10 mg/kg/day was administered via gavage for 7 days postoperatively. Group 4: Simvastatin 10 mg/kg/day was administered via gavage for 7 days preoperatively. R-A was performed after I-R. Simvastatin 10 mg/kg/day was administered via oral gavage also for 7 days postoperatively. The rats in all postoperative groups were fed with standard rat food and water. On postoperative day 8, all rats were prepared for surgery like the first surgical procedure and the abdomen was opened over the former incision.

Then, the rats were sacrificed with high-dose ketamine and the colonic segment was removed in such a manner that it would include 2 cm distal and proximal of the anastomosis and the anastomosis would be in the middle of the resected segment. One end of the colonic segment was secured using 2/0 polyglactin and the other end was secured to the infusion pump using 16 G catheter and then isotonic saline solution was infused at 2 ml/min. The intraluminal pressure was monitored and measured until there was a leak from the anastomotic region, and the pressure found was recorded as the anastomotic bursting pressure. The wet tissue samples from the anastomotic region were weighed. Then, the samples were dried for 3 days at 60 °C. Dry tissue samples were also weighed. The tissues were hydrolyzed for 8 h at 110 °C in 7 N hydrochloric acid (HCL) and were centrifuged for 20 min at 5000 rpm to obtain the study material. The absorbance of the material formed was evaluated colorimetrically (photometric) at 121 °C at 562 nm and the tissue hydroxyproline level was calculated.

The statistical analyses were performed using Statistical Package for Social Sciences (SPSS) for Windows® 17.0 package. Considering the small size of the samples included in the study, Kruskal Wallis analysis and the Mann–Whitney U test were used. Spearman's test was used to assess correlation.

The results were evaluated at a 95 % confidence interval and significance was evaluated at $p < 0.05$.

Results

There were no complications such as bleeding, anastomosis leak, fistula, or abscess in any of the groups. The animals that died during the operation and in the early postoperative period were replaced.

The mean anastomotic bursting pressure of the groups was 228.7 ± 22.6 mmHg for Group 1, 171.4 ± 15.4 mmHg for Group 2, 214.6 ± 20.3 mmHg for Group 3, and 207.3 ± 16.0 mmHg for Group 4 (Fig. 1). There was a statistically

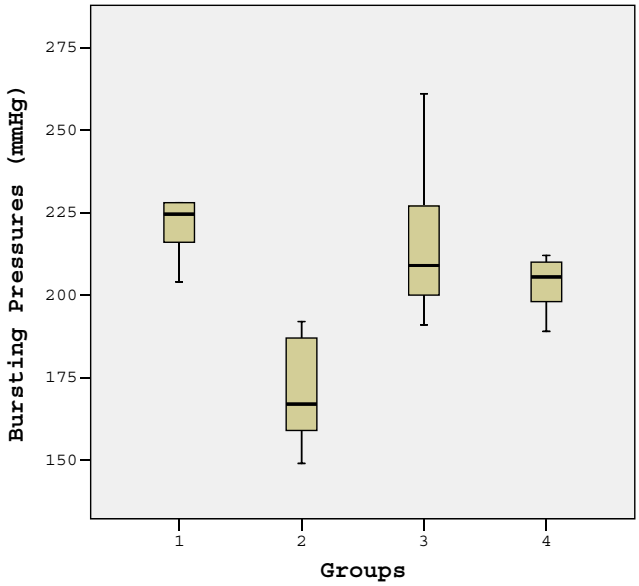

Fig. 1 Mean anastomosis bursting pressures of the groups

significant difference in anastomotic bursting pressures between the groups ($p < 0.001$) (Table 1).

When the mean anastomotic bursting pressures between the groups were analyzed, there was a statistically significant difference in the mean anastomotic bursting pressures in all comparisons between the groups ($p = 0.001$ between Group 1 and Group 2, $p = 0.009$ between Group 1 and Group 4, $p < 0.001$ between Group 2 and Group 3, and $p < 0.001$ between Group 2 and Group 4). There was no statistically significant difference in the mean anastomotic bursting pressures between Group 1 and Group 3 and between Group 3 and Group 4 ($p = 0.130$ and $p = 0.344$, respectively).

The mean tissue hydroxyproline level of the groups was 10.9 ± 3.7 mg OH-P/g dry tissue for Group 1, 5.1 ± 2.4 mg OH-P/g dry tissue for Group 2, 10.4 ± 6.2 mg OH-P/g dry tissue for Group 3, and 6.2 ± 3.5 mg OH-P/g dry tissue for Group 4 (Fig. 2). There was a statistically significant difference in the mean tissue hydroxyproline levels between the groups ($p = 0.013$) (Table 2).

When the mean tissue hydroxyproline levels between the groups were analyzed, there was a statistically significant difference in the mean tissue hydroxyproline level between Group 1 and Group 2 and between Group 1 and Group 4 ($p = 0.003$ and $p = 0.016$, respectively). There was no statistically significant difference in the mean tissue hydroxyproline levels in all other paired comparisons between the groups ($p = 0.650$ between Group 1 and Group 3, $p = 0.059$ between Group 2 and Group 3, $p = 0.650$ between Group 2 and Group 4, and $p = 0.112$ between Group 3 and Group 4).

There was a rather weak correlation for anastomotic bursting pressure and tissue hydroxyproline levels ($r = 0.25$, $p = 1$) (Fig. 3).

Discussion

Systemic and local factors are involved in the healing of anastomosis. Some of the systemic factors impairing the healing of anastomosis include anemia, hypovolemia, low partial pO2, low O_2 saturation, chronic diseases like atherosclerosis, chronic renal failure, diabetes, chronic pulmonary obstructive disease, neutropenia, malnutrition, vitamin deficiency, zinc deficiency, high-dose corticosteroids, and uremia [3]. Local factors may be listed as infections, intestinal content, prophylactic antibiotics, suture techniques, suture materials, radiation, and mesenteric vascular occlusion [11].

Several experimental and clinical studies suggested many factors to impair the healing of anastomosis and to cause leaks. It was shown that the healing of anastomosis was delayed and impaired in the intestinal segment with exposure to I-R injury [13–15]. It is reported that the reactive oxygen species are generated at a high amount during I-R and these molecules increase, especially during reperfusion, and therefore, intestinal tissue damage also occurs during reperfusion. Free oxygen radicals are produced as a consequence of events such as sepsis, ischemia reperfusion, and inflammation.

There are a number of scavengers for reactive oxygen species. This group is named as antioxidants though their chemical properties and actions are quite diverse. Antioxidants can be endogenous such as superoxide dismutase, catalase, glutathione, glutathione peroxidase, glutathione reductase, glutathione transferase, thioreductase, and uric acid. Superoxide radical is reduced to final products of water and oxygen by consecutive actions of superoxide dismutase and catalase. Glutathione, glutathione reductase, and glutathione peroxidase reduce hydrogen peroxide to water and regulate the redox potential in the cell [6].

Vitamins A, C, and E, folate, B vitamins, polyphenolic compounds, and minerals are dietary antioxidants. Vitamin C oxides to inactive dehydrosorbate while eliminating free oxygen radicals. Vitamin E prevents lipid peroxidation and by donating a hydrogen ion converts free radicals to less reactive forms [6]. Lycopene, the precursor of β-carotene, is a

Table 1 Mean anastomosis bursting pressures of the groups

	Group 1 mean ± SD	Group 2 mean ± SD	Group 3 mean ± SD	Group 4 mean ± SD	*p*
Anastomosis bursting pressures (mmHg)	228.7 ± 22.6	171.4 ± 15.4	214.6 ± 20.3	207.3 ± 16.0	<0.001

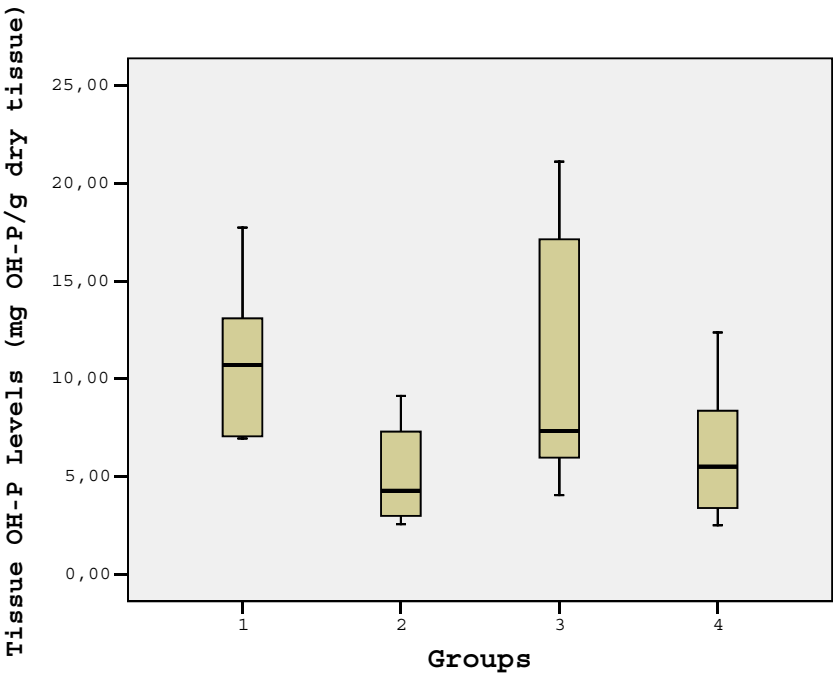

Fig. 2 Tissue hydroxyproline levels of the groups

highly potent scavenger of singlet oxygen. Folate and other B vitamins are important for glutathione production. Folate also scavenges hydroxyl and lipid peroxyl radicals in vitro. Polyphenols chelate metal ions like iron and copper which are known to act as pro-oxidants. Polyphenols also inhibit the action of xanthine oxidase [6].

Allopurinol and *n*-acetylcysteine are drugs with antioxidant properties [6]. Allopurinol inhibits xanthine oxidase, the enzyme which catalyzes the conversion of hypoxanthine to uric acid. It is regarded as an antioxidant specific for xanthine oxidase. N-acetylcysteine serves as a substrate in glutathione synthesis [6].

Simvastatin is also known to have antioxidant effect. Rugale et al. showed that simvastatin decreased superoxide anion production and increased both catalase and glutathione in cardiac tissue [16].

The present study about simvastatin was conducted in consideration of the role of the oxidative mechanisms during the ischemia and that the antioxidant system might play a critical role in the solution of this clinical problem.

The study by Karadeniz et al. demonstrated that the use of simvastatin upon anastomosis had a positive effect on the wound healing as in the present study and was effective through higher colonic anastomosis bursting pressures and higher tissue hydroxyproline levels [17].

The study by Rego et al. showed that simvastatin had a positive effect on wound healing in infected wounds by acting like an antibacterial agent due to its anti-inflammatory effects [18]. Another experimental study by Pruefer et al. demonstrated that simvastatin reduced the effect of staphylococcus aureus alpha toxin by guiding the exotoxin-leukocyte-endothelial cell interaction [19]. This suggests that simvastatin has a positive effect by reducing the bacterial colonization in the anastomotic region and accelerating wound healing.

In this experimental study, the highest bursting pressure was in the control group (Group 1). The bursting pressure closest to the control group was found in Group 3 (postoperative simvastatin group). The bursting pressure in the preoperative + postoperative simvastatin group (Group 4) was lower than the postoperative simvastatin group (Group 3). Tissue hydroxyproline levels showed similar results.

Statins have pleitropic effects. They are anti-inflammatory and immunomodulatory. Statins are also known for their endothelial dysfunction correcting effects as well as their antagonism for procoagulant activity and platelet functions [20, 21]. Stimulation of vascular endothelial growth factor and

Table 2 Mean tissue hydroxyproline levels of the groups

	Group 1 mean ± SD	Group 2 mean ± SD	Group 3 mean ± SD	Group 4 mean ± SD	*p*
Tissue hydroxyproline levels (mg OH-P/g dry tissue)	10.9 ± 3.7	5.1 ± 2.4	10.4 ± .2	6.2 ± 3.5	0.013

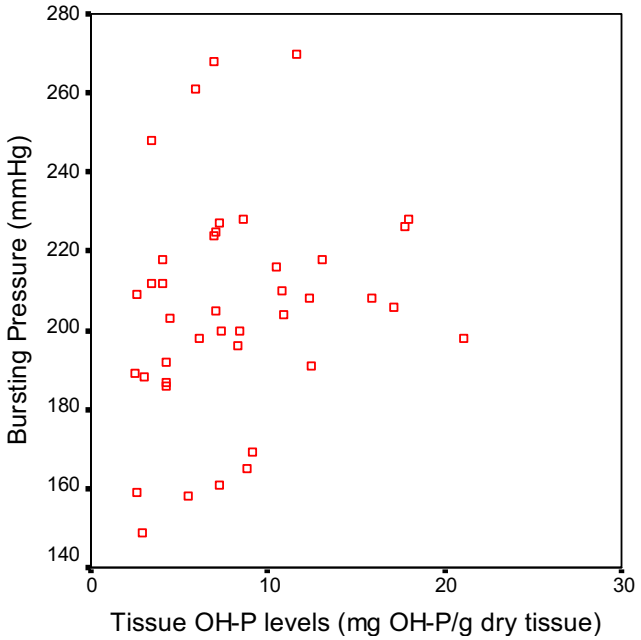

Fig. 3 Correlation of anastomotic bursting pressures and tissue hydroxyproline content

reduction in matrix metalloproteinase activity are other effects of simvastatin. In order to understand which property or properties of simvastatin have resulted in the finding of the higher bursting pressures and the higher tissue hydroxyproline levels in the simvastatin administered groups, further experiments are necessary [22–25]. Malondialdehyde, paraoxonase levels, VEGF, CRP, and other modulators of inflammation can be measured to verify the route of action of simvastatin on colonic anastomosis impaired by I-R injury [21–25].

Simvastatin is administered 5–40 mg daily in human. It has different regimens for different clinic situations and is increased to 80 mg/day only in a small group of patients who have been taking the drug >12 consecutive months without evidence of myopathy. The dosage of simvastatin administered to rats in this experiment is higher than the uppermost dosage given to humans [16]. Statins are also known to exhibit different activity when given in different dosage. They are pro-angiogenic at low doses whereas anti-angiogenic effect dominates at higher doses [25]. Therefore, measurement of blood levels of simvastatin can clarify the effect of dose on simvastatin action in this experimental setting.

In this study, it was also found that the postoperative administration of simvastatin regressed the extent of I-R injury. However, the preoperative and postoperative administration of simvastatin did not show the same effect. This is very likely to have resulted from the reduced proinflammatory cytokines upon the use of statin [26]. Furthermore, HMG-CoA inhibitors reduce the release of various chemoreactant molecules through the nuclear factor kappa-β. With the statin treatment, the COX-2 synthesis, which has a significant place in inflammation, is also reduced. Other than adhesion and infiltration, statins also inhibit the production of matrix metalloproteases of the inflammatory cells. Statins inhibit both vascular and systemic inflammation in this way. HMG-CoA inhibitors also inhibit the CRP synthesis. CRP impairs the endothelial functions by reducing the endothelial eNOS expression in the endothelial cells [21, 27–33]. After the administration of HMG-CoA inhibitors, the release of endothelin-1, a strong vasoconstrictor produced by the endothelial cells with a role in vascular tonus and cell proliferation, is also reduced [34–36]. We believe that the preoperative administration of simvastatin prevents the healing of anastomosis and production of hydroxyproline. This assumption can be verified by measuring inflammatory and anti-inflammatory parameters.

Statistical analysis revealed a rather weak correlation for anastomotic bursting pressure and tissue hydroxyproline levels ($r = 0.25$, $p = 1$). This situation can be explained by the fact that although commonly used as a surrogate parameter for wound healing, hydroxyproline is not the sole parameter for evaluating wound healing. In addition to this, the small size of the study groups may have a role in this result for correlation.

Conclusion

In this study, it was found that postoperative oral administration of simvastatin reduced the potential adverse effects in I-R injury as anastomotic bursting pressures and tissue hydroxyproline levels were restored nearly to that of the control group in which I-R was not applied. Combined preoperative and postoperative administration of simvastatin was not found to be effective on reducing the I-R injury.

Before suggesting simvastatin administration in colonic anastomosis in the setting of intestinal I-R injury in humans, further experimental studies are necessary in order to reveal the mechanisms and dosage by which simvastatin improves healing of colonic anastomosis after I-R injury.

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