



Sildenafil citrate improves microvascular density and healing in remnant gastric tissue after sleeve gastrectomy- An experimental study

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Abstract

Purpose: Obesity is a chronic, systemic, and multifactorial disease characterized by high morbidity rates. Sleeve gastrectomy (SG), one of the most frequently performed bariatric procedures, is a restrictive surgery where approximately 80% of the stomach is resected. Anastomotic leakage is one of the most fatal complications of this procedure, where tissue perfusion and healing play a critical role in prevention. This study aims to evaluate the effects of sildenafil citrate (SC), a phosphodiesterase type 5 (PDE-5) inhibitor, on microcirculation and oxidative stress parameters in the remnant gastric tissue following surgery.

Method: Twenty male Wistar albino rats were randomly divided into two groups: Control (SG) (n=10) and Experimental (SG+SC) (n=10). The control group received oral saline, while the experimental group was administered 10 mg/kg/day of sildenafil citrate for five days. On the fifth day, the rats underwent gastrectomy, and the remnant gastric tissues were analyzed biochemically and histopathologically. To evaluate oxidative stress, levels of nitric oxide (NO), malondialdehyde (MDA), catalase (CAT), superoxide dismutase (SOD), total antioxidant capacity (TAC), total oxidant status (TOS), and glutathione (GSH) were measured using ELISA kits.

Findings: Sildenafil citrate treatment led to a significant decrease in TOS, oxidative stress index (OSI), and MDA levels compared to the control group. Conversely, a significant increase was observed in the antioxidant markers CAT, GSH, and SOD. Histopathological examinations revealed lower levels of vascular dilatation, edema, and inflammation in the SC group, while microvascular density (Anti-CD34 positivity) was significantly higher.

Conclusion: Sildenafil citrate contributes to tissue repair by suppressing oxidative damage and improving angiogenesis and microcirculatory hemodynamics in the operated gastric tissue. These findings suggest that SC may serve as a potential therapeutic agent in maintaining tissue integrity and reducing the risk of leakage complications following bariatric surgery.

Keywords: sleeve gastrectomy; morbid obesity; bariatric surgery; sildenafil citrate

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Sildenafil sitrat, tüp mide ameliyatı sonrası remnant mide dokusunda mikrovasküler yoğunluğu ve iyileşmeyi artırır - Deneysel bir çalışma

Özet

Amaç: Obezite, morbidite oranı yüksek, sistemik ve çok faktörlü kronik bir hastalıktır. Günümüzde en sık uygulanan bariatrik cerrahi yöntemlerinden biri olan tüp mide ameliyatı (sleeve gastrektomi - SG), midenin yaklaşık %80'inin rezeke edildiği kısıtlayıcı bir prosedürdür. Bu cerrahinin en mortal seyreden komplikasyonlarından biri olan anastomoz kaçağını önlemede doku perfüzyonu ve iyileşmesi kritik rol oynar. Bu çalışma, bir fosfodiesteraz tip 5 (PDE-5) inhibitörü olan sildenafil sitratın (SC), cerrahi sonrası mide kalıntı dokusundaki mikrosirkülasyon ve oksidatif stres parametreleri üzerindeki etkilerini değerlendirmeyi amaçlamıştır.

Metod: Çalışmada 20 adet erkek Wistar albino sıçan; Kontrol (SG) (n=10) ve Deney (SG+SC) (n=10) olmak üzere iki gruba ayrıldı. Kontrol grubuna oral serum fizyolojik, deney grubuna ise 5 gün boyunca 10 mg/kg/gün sildenafil sitrat uygulandı. Beşinci günde gastrektomi uygulanan deneklerin remnant mide dokuları biyokimyasal ve histopatolojik açıdan incelendi. Oksidatif stres değerlendirmesi için nitrik oksit (NO), malondialdehit (MDA), katalaz (CAT), süperoksit dismutaz (SOD), toplam antioksidan kapasite (TAC), toplam oksidan durumu (TOS) ve glutatyon (GSH) seviyeleri ELISA yöntemiyle ölçüldü.

Bulgular: Sildenafil sitrat tedavisi, kontrol grubuna kıyasla TOS, oksidatif stres indeksi (OSI) ve MDA seviyelerinde anlamlı bir azalma sağladı. Buna karşılık antioksidan göstergelerden CAT, GSH ve SOD seviyelerinde anlamlı artış saptandı. Histopatolojik incelemelerde, SC grubunda vasküler dilatasyon, ödem ve inflamasyonun daha düşük olduğu, mikrovasküler yoğunluğun (Anti-CD34 pozitifliği) ise anlamlı derecede arttığı belirlendi.

Sonuç: Sildenafil sitrat, cerrahi uygulanan mide dokusunda oksidatif hasarı baskılayıp anjiyogenezi ve mikrosirkülasyon hemodinamiğini iyileştirerek doku onarımına katkı sağlamaktadır. Bu bulgular, SC'nin bariatrik cerrahi sonrası doku bütünlüğünü korumada ve olası kaçak komplikasyonlarını azaltmada potansiyel bir terapötik ajan olabileceğini göstermektedir.

Anahtar kelimeler: sleeve gastrektomi; morbid obezite; bariatrik cerrahi; sildenafil sitrat

1. Introduction

Obesity has become a critical public health problem and causes a serious economic burden for the world [1]. In recent years, the prevalence of obesity is increasing in underdeveloped and developing countries as well as in developed countries[2]. It was reported that approximately 30% of the world's population is overweight or obese[3]. Obesity primarily affects the cardiovascular and endocrine systems, as well as the gastrointestinal system [4]. Although obese patients lose weight with non-surgical methods, in most cases they regain the lost weight. For this reason, the bariatric surgery technique is considered the most effective method in which a loss of 30-70% of body weight can be maintained long term[5]. Previous studies showed that patients who underwent bariatric surgery lost 60-80% of their excess weight within 2 years post-surgery [6]. The Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (LSG) surgeries are the most common surgical procedures. Sleeve gastrectomy (SG) is the preferred surgical alternative to achieve appropriate weight loss and improve the inflammatory profile in obesity. Anastomotic leakage, one of the most feared and fatal complications of SG, is seen in 0-7% of patients; however, LSG has some primary advantages over other bariatric surgical methods such as no risk of internal herniation, no need for intestinal bypass surgery, a shorter operation time, no need for foreign body implantation, and protection from metabolic disorders [7]. Moreover, LSG has become increasingly popular in recent years since it provides significant weight loss by enabling the loss of more than 60% excess weight in 3-year follow-ups and it is technically simple compared to other surgical methods [8]. In morbid obesity, proinflammatory cytokines are highly expressed and cause systemic inflammation resulting in dysfunction in adipose tissue and an increase in oxidative stress. In various clinical studies, it was stated that there is a positive correlation between obesity and the end products of free radicals such as F2-isoprostanese, malondialdehyde (MDA), and lipid hydroxyperoxidase, which are oxidative stress indicators. Some studies reported that there is a positive correlation between body mass index (BMI) and free radicals resulting from oxidative stress[9].

Sildenafil citrate (SC) has been used since 1985 due to its anti-hypertensive properties. It is a phosphodiesterase type 5 inhibitor (PDE5i) that prevents the degradation of cyclic guanosine monophosphate (cGMP), increases the effects of nitric oxide (NO), and causes blood vessel relaxation [10]. It was approved for the treatment of erectile dysfunction in 1998 and pulmonary hypertension in 2005. Positive effects of sildenafil on anastomosis, bone, skin, and facial recovery have been reported in some animal studies, case reports, and clinical studies[11]. Sildenafil has beneficial effects on the wound healing process through different mechanisms, including the increase of microcirculation hemodynamics, the stimulation of angiogenesis, the induction of apoptosis of adhesion fibroblasts, and the reduction of inflammatory responses through inhibition of vasodilation, platelet aggregation, and adhesion [10]. cGMP is a key secondary messenger, which is synthesized by guanylases from guanosine triphosphate (GTP) and is involved in many cellular events and processes. Various studies showed that cGMP has an anti-inflammatory effect and

that it also activates anti-apoptotic pathways. Many studies reported that sildenafil has antioxidant, anti-inflammation, and anti-apoptotic effects by inducing cGMP accumulation and, therefore, it may be a potential therapeutic agent for the treatment of many diseases [12].

Considering this information, this study aimed to determine the effects of SC supplementation on oxidative stress parameters at the stomach anastomotic tissue level and compare microvascular density.

2. Materials and methods

Experimental studies were conducted at the Eskişehir Osmangazi University Medical and Surgical Experimental Animal Application and Research Center, in accordance with the "National Health Institutes Guidelines on the Care and Use of Laboratory Animals".

2.1. Animals

In this experimental study, twenty 4-month-old healthy male Wistar albino rats weighing 300 - 350g were used. Both preoperatively and postoperatively, subjects were fed standard laboratory chow and tap water under constant environmental conditions (temperature: 23°C and humidity: 55.5%).

The rats were randomly divided into 2 groups. The control group (SG) (n=10) rats were only given oral 0.9% NaCl via a feeding tube and a sleeve gastrectomy was then performed. The rats were sacrificed on the fifth day. The experimental group (SG+SC) was given 10 mg/kg/day SC orally via a feeding tube for 5 days before the SG and the SG procedure was then performed. The dose of 10 mg/kg was inspired by the study of Cakir et al. on colon anastomoses. Sildenafil citrate was dissolved in distilled water with a minimum amount of HCl and adjusted to a final pH of approximately 4 with NaOH. The rats were sacrificed on the fifth day.

2.2. Surgical Procedure

To prepare for the SG, the gastrosplenic ligament and omentum majus of the rats were tied with 3-0 silk sutures under anesthesia (60 mg/kg ketamine i.m. and 10 mg/kg xylazine i.p.) and the stomach of each rat was freed up to the pylorus. The SG was performed on the resection area (approximately 70% of the stomach), covering most of the fundus, with vascular forceps. Remnant gastric resection margins were manually sutured with continuous inverting polyglactin 910 (Vicryl® 5-0; Ethicon, São Paulo) (Schimieden pattern). At the end of the surgery, 10 ml of Ringer's lactate solution were injected intraperitoneally to prevent dehydration. The abdomen was then closed. After the procedure, the rats were given water daily from the 4th hour. After continuing the oral feeding, all animals were given a liquid diet (10% dextrose) for 3 days and standard chow for the remaining 2 days. In the postoperative period, 1-2 mg/kg of meloxicam was administered subcutaneously as an analgesic. The health status of the rats was observed daily.

After the midline laparotomy, followed by full-layer wedge resections including the gastric anastomosis line under anesthesia on the 5th postoperative day, the tissue was divided into two equal sections passing through the middle of the anastomosis. One section was placed in a 10% formaldehyde solution for histopathological examination. The other section was frozen at -80°C for the measurement of the oxidative stress markers. Subsequently, the rats were sacrificed using the intracardiac blood collection method.

2.3. Biochemical Analyses

All tissues were homogenized in PBS (pH: 7.4). Then the homogenates were centrifuged at 10,000 rpm for 2 minutes at +4°C. Total oxidant status (TOS-RelAssay Diagnostic, Turkey), total antioxidant capacity (TAC- RelAssay Diagnostic, Turkey), nitric oxide (NO- Sigma Aldrich, Germany), malondialdehyde (MDA- Sigma Aldrich, Germany), catalase (CAT- Sigma Aldrich, Germany), glutathione (GSH- Sigma Aldrich, Germany), and superoxide dismutase (SOD- Sigma Aldrich, Germany) levels in the supernatant were measured as specified in commercial ELISA kit procedures.

MDA tissue levels were measured in homogenized tissue at a ratio of 1:10 (weight:volume) in a cold 1.15% KCl solution following the thiobarbituric acid method and the results were given in nmol/g tissue weight. NO levels were measured using the Griess diazotization reaction method after the conversion of nitrate to nitrite using nitrate reductase in the supernatant. The color formed in the reaction server was read at a wavelength of 540 nm in a spectrometer and then plasma NO levels were indirectly calculated according to the calibration curve prepared using nitrite standards. Tissue NO activity results were determined as $\mu\text{mol/L}$. Catalase (CAT) activity was determined using a method described by Goth [13]. Oxidative stress markers, including catalase (measured in kU/L), SOD, MPO, MDA, GSH, and ROS, were quantified using commercial assay kits (Nanjing Jiancheng Biological Engineering Institute, China) following the manufacturer's protocols. Briefly, frozen tissue samples were homogenized and centrifuged at 1000g for 20 minutes to isolate the supernatant. After equilibrating reagents to room temperature, 100 μL of standards or samples were loaded into the wells and incubated at 37°C for 2 hours. Following liquid removal, 100 μL of Solution A was

added, and the plates were incubated for an additional hour at 37°C. After three wash cycles, 90 µL of substrate solution was added to each well. The plates were then covered with a protective membrane and developed in the dark at 37°C. The reaction was halted using 50 µL of stop solution, and the optical density (OD) was immediately recorded at 450 nm using a microplate reader. All assays were performed in triplicate to ensure reproducibility.

The Calculation of the Oxidative Stress Index (OSI)

The ratio of TOS to TAC was accepted as the oxidative stress index (OSI). For calculation, the resulting TAC unit was converted to µmol/L and the OSI value was calculated according to the following formula: OSI (arbitraryunit) = TOS (µmol H₂O₂ equivalent/L) / TAC (µmolTroloxequivalent/L) [14].

2.4. Histochemistry and Immunohistochemistry

Wedge resection material of the esophagogastric junction (EGJ) area near the SG area was put in a 10% formaldehyde solution and paraffin blocks were prepared from the stored tissue sections. For all groups, sections of 5µ thickness were stained with hematoxylin-eosin (HE) and Anti-CD34 and examined under a light microscope by a single pathologist. Sections were stained with HE and examined under a light microscope (Olympus BX51). Signs of epithelial damage, inflammation, vascular dilatation, and edema were evaluated morphologically. Morphological findings were ranked as score 0 if absent, score 1 if mild, score 2 if moderate, and score 3 if severe [15].

CD34 is a transmembrane phosphoglycoprotein and is frequently used to examine neovascularization. In this experiment, immunohemagglutination (IHA) tests were performed as described in the literature after staining with anti-CD34 (Thermo Fisher Scientific – USA). The tissues of each rat were examined in 5 different magnification fields (x400) (large magnification areas – LMA). Quantitative vessel count was performed using the method described by Vermeulen et al. for the assessment of microvessel density (MVD) (number/mm²) [27]. The number of vessels stained with anti-CD34 was scored as 1, 2, or 3 positive (1 positive (+) = 10-24 vessels/LMA; 2 positive (++) = 25-49 vessels/LMA; 3 positive (+++) = 50 or more vessels/LMA).

2.5. Statistical Analysis

Statistical analysis was performed in the IBM SBSS version 21 software program. The fitness of the quantitative variables to a normal distribution was investigated using the Shapiro-Wilk W test. The t-test was performed for descriptive statistics and the normally distributed quantitative data of the two groups and the Mann Whitney-U test was used for non-normally distributed quantitative data. Descriptive statistics of the groups were presented as the mean ± standard deviation or as the median (Q1-Q3). A *p*-value of <0.05 was considered statistically significant.

3. Results

3.1. Biochemical Results

The total antioxidant level in the stomach tissue did not change with SC treatment (*p*=0.63) whereas the total oxidant level decreased significantly (*p*<0.001). Tissue nitric oxide levels significantly decreased (*p*<0.001) and tissue catalase and glutathione levels increased significantly in the SC group compared to the control group (*p*<0.001) (Table 1). The OSI and the malondialdehyde level decreased significantly in SC-administered rats compared to the control group (*p*<0.001), while there was a significant increase in the superoxide dismutase levels (*p*<0.001) (Table 1). This result indicates that sildenafil protects against increased oxidative stress after an SG. The unchanged total antioxidant level may be due to the dose of SC administered.

Table 1. Comparison of tissue antioxidant levels

	Control (SG) (n=10)	Experimental Group (SG+SC) (n=10)	p
TAC (µmolTroloxEq/L)	1.01 SD0.23	0.95 SD0.31	0.63
TOS (µmol H ₂ O ₂ Eq/L)	4.61 SD1.24	2.57 SD0.98	<0.001
NO (µmol/L)	2.44 SD0.18	2.11 SD0.04	<0.001
CAT (kU/L)	49.97 SD8.69	146.30 SD56.62	<0.001
GSH (µg/L)	1.07 SD0.14	1.97 SD0.14	<0.001
OSI	0.45 SD0.07	0.24 SD0.06	<0.001
SOD (kU/L)	184.70 SD8.21	198.20 SD3.65	<0.001
MDA (nmol/g)	0.56 SD0.03	0.36 SD0.13	<0.001

TAC: Total Antioxidant Capacity, TOS: Total Oxidant Status, NO: Nitric Oxide, CAT: Catalase, GSH: Glutathione, OSI: Oxidative Stress Index, SOD: Superoxide dismutase, MDA: Malondialdehyde. Values are given as mean ± standard deviation.

3.2. Histopathologic Results

The EGJ area near the SG area in both the control and experimental groups was stained with HE and examined using light microscopy. No epithelial damage was detected in any of the sections of the two groups. The vessels in the control group (2.70 SD0.48) were more dilated compared to those in the SC-administered group (1.30 SD0.48) ($p < 0.001$). Similarly, edema observed in the control group (2.70 SD0.48) was significantly more intense than in the SC group (0.90 SD0.57) ($p < 0.001$). According to the inflammation scoring, there was significantly more intense inflammation in the control group (SG) (2.50 SD0.53) (SG+SC = 0.70 SD0.48, $p < 0.001$) (Table 2). The tunica mucosa layer of the control group showed a histological appearance close to the normal rodent gastric mucosa; however, edema, vascular dilatation in the tunica submucosa layer, and lymphocytic infiltration findings were more intense. Moreover, there was no damage in the tunica muscularis layer (Figure 1).

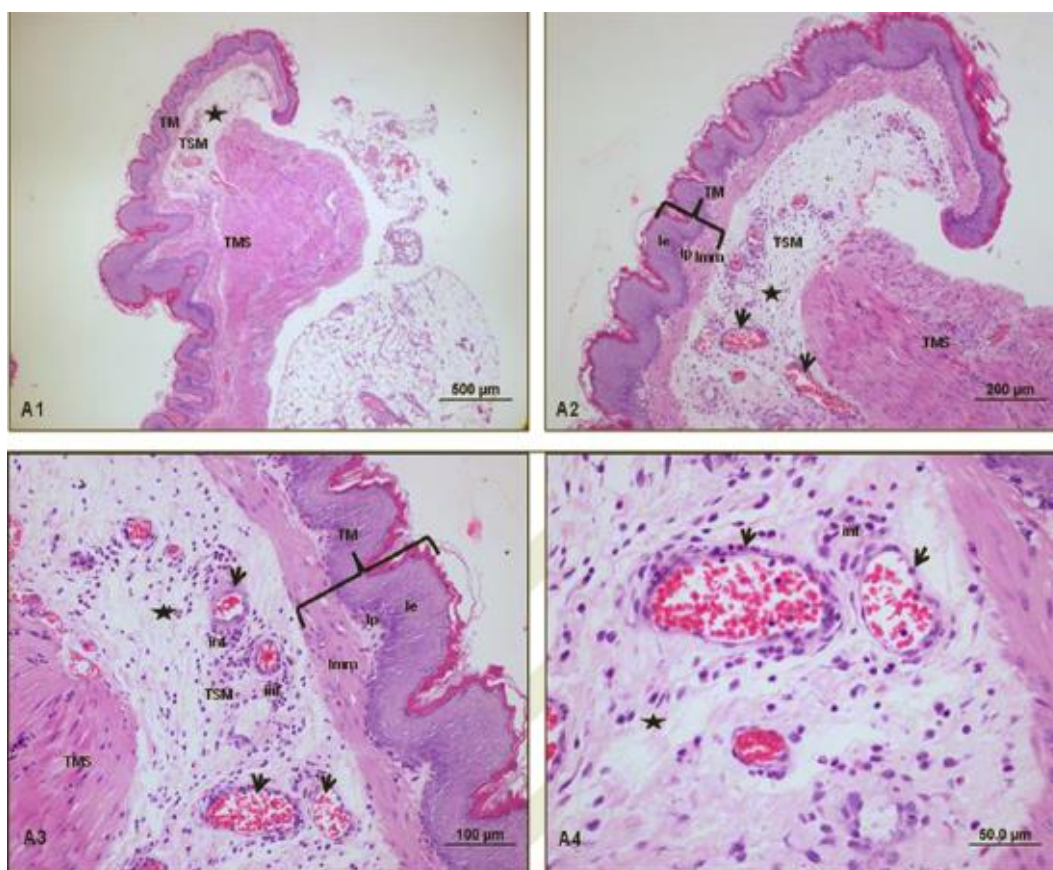


Figure 1. Light microscopic image of EGJ in the control group at different magnifications. The tunica mucosa (TM) layer with lamina epithelialis layer (le), lamina propria (lp) and lamina muscularis mucosa (lmm) layers with multi-layered non-keratinized squamous epithelium structure is observed to be close to normal. In the tunica submucosa layer (TSM), significant edema (*), vascular dilatation (→) and cellular infiltration (inf) are observed. The tunica muscularis layer (TMS) is observed to be close to normal (H-E, Scales are 500 µm for A1, 200 µm for A2, 100 µm for A3 and 50 µm for A4)

Table 2. Comparison of histopathological parameters

	Control (SG) (n=10)	Experimental Group (SG+SC) (n=10)	p
Edema Score	2.70 SD0.48	0.90 SD0.57	<0.001
Dilatation Score	2.70 SD0.48	1.30 SD0.48	<0.001
Inflammation Score	2.50 SD0.53	0.70 SD0.48	<0.001

Histopathological examination findings (Morphological findings: score 0 if absent, score 1 if mild, score 2 if moderate, and score 3 if severe). Values are given as mean ± standard deviation.

The tunica mucosa and muscularis layers were normal in SC-administered animals. The damage in the tunica submucosa (edema, vasodilation, and inflammation) due to the surgery was milder than in the control group (Figure 2).

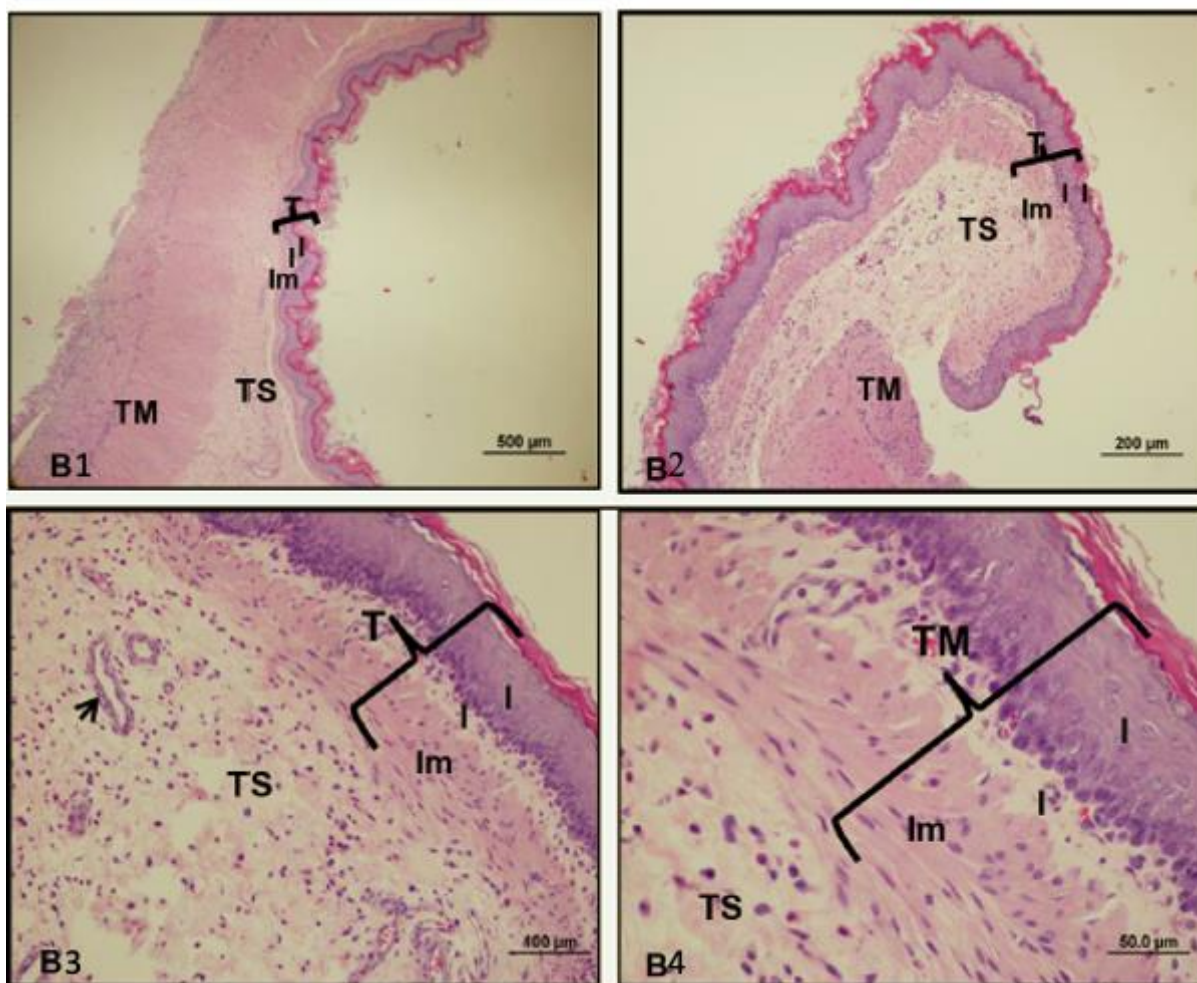


Figure 2. Light microscopic images of EGJ at different magnifications in the experimental (sildenafil citrate) group. The tunica mucosa (TM) layer with lamina epithelialis layer (le), lamina propria (lp) and lamina muscularis mucosa (lmm) layers with multilayered non-keratinized squamous epithelium structure is observed to be close to normal. Decreased edema (*) and normal vascular structures (→) are seen in the tunica submucosa layer (TSM) compared to the control group. The tunica muscularis layer (TMS) is observed to be close to normal (H-E, Scales are 500µm for B1, 200µm for B2, 100µm for B3 and 50µm for B4)

3.3. Immunohistochemical result

Vessels stained with anti-CD34 in the transition area of the esophagus and stomach (EGJ) showed newly developed vessels. There was a moderate CD34 expression in the control group but a high CD34 expression in the experimental group (Figure 3). In this area, the microvascular density (MVD), counted in 5 different magnification fields, was significantly higher in the experimental group (53.50 SD2.55) compared to the control group (26.20 SD8.23) ($p < 0.001$; Table 3). According to the scoring of the anti-CD34 staining of the vessels in this area, the vessels in the experimental group (3.00 SD0.00) showed a higher CD34 expression compared to the control group (1.60 SD0.52) ($p < 0.001$; Table 3). It is evident that SC stimulates angiogenesis after a sleeve gastrectomy.

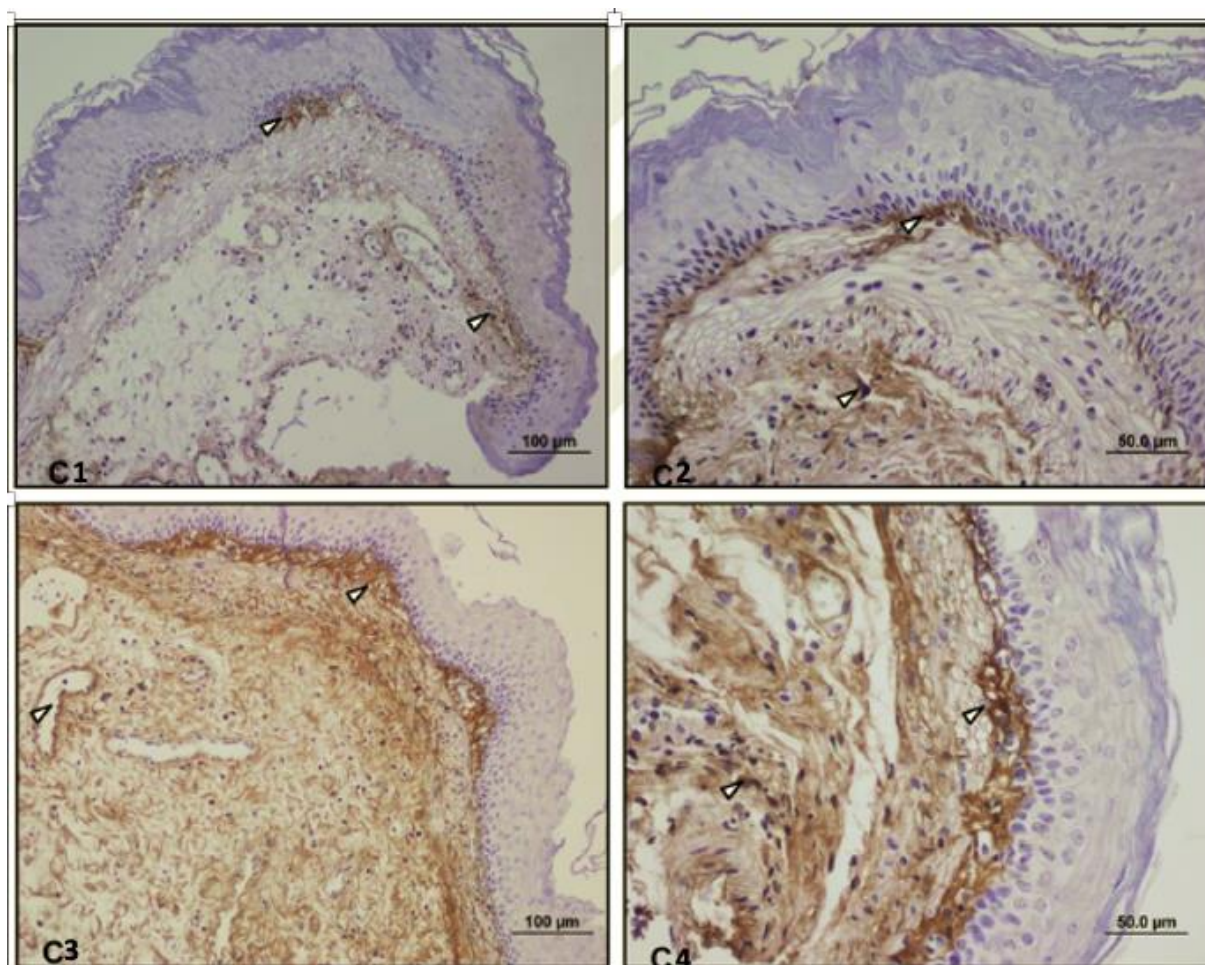


Figure 3. Anti-CD34 staining images. In the control group, following anti-CD34 staining, moderate CD34 positive stained cells (▶) are noticeable in the vascular structures (Top). In the sildenafil citrate group, intense CD34 positive stained cells (▶) are noticeable (Bottom). The scale for the images on the left is 100µm and the scale for the images on the right is 50.0µm.

Table 3. Anti-CD34 staining findings in the control and experimental groups in EGJ

Anti-CD34 staining pattern	Control Group (SG) (n=10)	Experimental Group (SG+SC) (n=10)
(+)	4 (% 40)	0
(++)	6 (% 60)	0
(+++)	0	10 (% 100)

Anti-CD34 stained vessels were scored in 5 different magnification fields (x400) (LMA): 10-24 vessels (+), 25-49 vessels (++), and 50 and over vessels (+++).

4. Conclusions and discussion

In this study, it was hypothesized that SC used to enhance sleeve gastrectomy surgery may contribute to wound healing by improving microcirculation hemodynamics. To investigate the effects of SC on wound healing in anastomotic stomach tissue, oxidative stress parameters on the perianastomotic tissue were measured. The EGJ area was evaluated in terms of histopathological findings and MVD levels. In this study, a statistically significant increase was observed in both MVD and antioxidant levels in gastric tissue after the administration of SC in sleeve gastrectomy surgery. It was observed that vascular dilatation, edema, and inflammation scores significantly decreased. As a result of the literature review, this study, based on all these findings, is the first to reveal the effect of SC on perianastomotic gastric tissue.

Inflammatory cell infiltration characteristically increases with an increased volume of adipocytes. Parameters such as excessive fat accumulation and increased cellular stress, hypoxia, metabolic dysfunction, and inflammation increase the oxidative load. Obesity is a worldwide public health problem. Diabetes, hypertension, hyperlipidemia, sleep apnea, and degenerative joint disease accompany obesity. Bariatric surgery provides the safest, most effective, and most successful treatment of morbid obesity since it quickly resolves long-term weight issues and accompanying diseases. SG is the most frequently performed bariatric procedure[16].

After a SG, leaks usually occur proximal to the incision surface, near the EGJ. Leaks after a sleeve gastrectomy are categorized as mechanical-tissue-related, usually occurring within 2 days, or ischemic, occurring within the first 5 postoperative days [17]. Successful wound healing and tissue regeneration depend on angiogenesis [18].

In the study conducted by Orman et al. on rats, it was observed that the EGJ had a lower MVD level than in a normal gastric corpus and that sleeve gastrectomy had no adverse effect on microvascular density of the EGJ [19].

SC is a phosphodiesterase type-5 inhibitor (PDE5i) that inhibits the degradation of cyclic guanosine monophosphate (cGMP), enhances the effects of nitric oxide (NO) and angiogenesis, and leads to the relaxation of blood vessels [10]. Clinically, angiogenesis occurs 3-5 days after injury at the initial wound bed [20]. In this study, the CD-34 reaction increased in rats treated with SC after an SG, suggesting that it increased angiogenesis and therefore could be a treatment agent for wound healing. In this study, the 5th postoperative day was selected for the evaluation of MVD, and MVD levels increased statistically significantly in the SC-administered group.

In the study conducted by Hasanoğlu et al. on rats, it was observed that colon anastomosis was stronger and wound healing was better in SC-administered groups [21]. Uzun et al. investigated the effects of SC on normal and ischemic colon anastomosis in a rat. In their study, it was reported that SC could positively affect the healing of ischemic anastomosis due to its possible effects on NO metabolism and lipid peroxidation [22]. In the study of Çakır et al., the effects of SC on anastomosis healing in an experimental high-risk colon anastomosis model created in rats was investigated and the study reported an increase in collagen content and epithelialization, a decrease in oxidative stress and neutrophil infiltration, and better mechanical strength after sildenafil treatment [23]. Ayten et al. found that sildenafil contributed positively to the healing of colon anastomosis and the reduction of adhesion in the presence of infection [24].

In this study, the number of dilated vessels in rats, which increased after a sleeve gastrectomy, decreased with a lower NO level after SC treatment. Furthermore, the MDA level, which is used to measure lipid peroxidation, decreased in the SC group. The increase in the oxidative stress level caused by the sleeve gastrectomy procedure decreased with SC administration. As supported by the literature, all these factors accelerated the wound healing process after the surgical procedure.

Bawahab et al. reported that the activities of antioxidant markers in plasma are high in morbidly obese individuals and that the presence of chronic inflammation and oxidative stress in obesity will result in an increase in superoxide radicals [25]. As a result of a compatible response, a decrease in SOD activity and weight loss achieved by sleeve gastrectomy reduce the stimulating effect on glutathione peroxidase (GPx), glutathione S-transferase (GST), vitamin C, and SOD by inhibiting the formation of ROS.

In this study, decreased SOD, catalase, and glutathione levels in rats that underwent a sleeve gastrectomy increased after SC administration, explaining the reason for the decreased total oxidant level in the tissue.

A statistically significant increase was observed in MVD and antioxidant levels in gastric tissue after the administration of SC in sleeve gastrectomy surgery. In this experimental study, it was seen that SC replacement therapy has protective effects on the incision line surface and may contribute to wound healing in sleeve gastrectomy. Such studies cannot be performed on humans; however, they are still valuable. Despite the limitations, these results may provide a new perspective which future work can be based on. Furthermore, as a result of the literature review, it can be suggested that this study is the first to reveal the effect of SC on perianastomotic gastric tissue.

Limitation of the study

Using immunohistochemistry to measure MVD levels may not yield optimal results for the evaluation of vascularity. Further work is needed to evaluate MVD levels using other methods such as the Western blot.

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Ethical statement: The experimental protocol was approved by the Eskişehir Osmangazi University Local Ethics Committee for Animal Experiments on November 14, 2019, with registration number 746.

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