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ORIGINAL ARTICLE

The Protective Effect of Sildenafil on Colon Anastomosis in a Rat Model Undergoing Hyperthermic Intraperitoneal Chemotherapy

Hipertermik İntraperitoneal Kemoterapi Uygulanan Sıçan Modelinde Sildenafilin Kolon Anastomozunu Koruyucu Etkisi

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ABSTRACT

Aim: This study aimed to investigate the effects of sildenafil on colonic anastomosis healing in rats treated with hyperthermic intraperitoneal chemotherapy (HIPEC).
Method: In our study, 30 Wistar-albino rats were used. 30 rats were divided into 3 groups: the sildenafil, control, and sham groups. Left colon anastomosis was performed on rats in all three groups. The HIPEC procedure was applied to the sildenafil group and control group. During the postoperative period, sildenafil was given orally to the sildenafil group. On the 7th day, the anastomotic loop was excised, and bursting pressure, and adhesion were evaluated. The anastomotic loop was evaluated histopathologically. The results were compared statistically.
Results: When the results were evaluated considering bursting pressure, and adhesion between the sildenafil group and control group, there was no difference. Considering adhesion, the sham group was superior to the other two groups. Histopathological examination reveals that the sham group was significantly superior to the other two groups in terms of anastomotic re-epitelization and muscle separation. There was a significant difference between the sildenafil group and the control group in terms of fibrosis and granulation.
Conclusion: On colon anastomosis performed together with HIPEC application, histopathologically positive effects of sildenafil were observed. The burst pressure of colon anastomosis was not significantly different.

Keywords: Anastomosis healing, colonic anastomosis, hyperthermic intraperitoneal chemotherapy, sildenafil

ÖZ

Amaç: Çalışmanın amacı hipertermik intraperitoneal kemoterapi uygulanan sıçanlarda kolon anastomozu iyileşmesi üzerine sildenafilin etkilerini araştırmaktır.
Gereç ve Yöntemler: Çalışmamızda 30 adet Wistar-albino cinsi sıçan kullanılmıştır. Sildenafil, kontrol ve sham grubu olmak üzere 3 grupta 10'ar sıçan kullanılmıştır. Tüm gruptaki sıçanlara sol kolon anastomozu yapıldı. Sildenafil grubu ve kontrol grubuna HIPEK işlemi uygulandı. Sildenafil grubuna postoperatif oral sildenafil verildi. 7. gün anastomoz ansı eksize edilerek patlama basıncı ve adezyon değerlendirildi. Anastomoz ansı histopatolojik olarak değerlendirildi. Sonuçlar istatistiksel olarak karşılaştırıldı.
Bulgular: Sonuçlar değerlendirildiğinde patlama basıncı ve adezyon açısından sildenafil grubu ile kontrol grubu arasında fark saptanmamıştır. Sham grubu ise adezyon açısından diğer iki gruba üstün görülmüştür. Histopatolojik incelemede ise sham grubunun anastomoz re-epitelizasyonu ve kas ayrışması açısından diğer iki gruba karşı anlamlı olarak üstün olduğu görülmüştür. Fibrosis ve granülasyon açısından sildenafil grubu ile kontrol grubu arasında anlamlı olarak farklılık saptanmıştır.
Sonuçlar: HIPEK uygulaması ile beraber yapılan kolon anastomozu üzerinde sildenafilin histopatolojik olarak olumlu etkileri görülmüştür. Kolon anastomozu patlama basınç açısından ise fark görülmemiştir.

Anahtar Kelimeler: Anastomoz iyileşmesi, hipertermik intraperitoneal kemoterapi, kolon anastomozu, sildenafil

Introduction

Anastomotic leakage after colorectal surgery is an important cause of mortality, morbidity, and prolonged hospital stays. Perioperative mortality is often caused by septicemia and peritonitis (1). The main causes of anastomotic leak are thought to be anatomical mismatch and suboptimal blood supply (2). In addition, surgical technique, intestinal integrity, anastomotic tension, drugs, and comorbid diseases can be considered. Even under optimal conditions, there is a significant risk of leakage in left colon and rectum surgeries (3).

Colorectal cancer with peritoneal metastasis is considered stage 4. The dose of medication required for the treatment of peritoneal metastases via intravenous chemotherapy is much greater than the normal dose. When the dose is administered intraperitoneally, it has a sufficient effect on tumor cells up to a sufficient tissue depth by diffusion, and systemic toxicity is avoided. Therefore, hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery are among the best treatment options for such patients (4).According to previous studies, the anastomotic burst pressure and collagen ratio in anastomotic tissue decrease when

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HIPEC is applied with mitomycin (3). Therefore, the risk of anastomotic leakage is predicted to increase in patients undergoing HIPEC.
Oral administration of sildenafil in anastomosed rats increases the strength of the anastomosis and increases burst pressure by affecting NO metabolism, which reduces oxidative stress by vasodilation and activates the nitrate-nitrite oxide pathway, one of the wound healing pathways (5-7).

In our study, the effectiveness of sildenafil citrate, which has previously been shown to increase tissue nitric oxide levels and increase anastomotic burst pressure and which is effective for enhancing anastomotic strength and burst pressure, on colon anastomosis, which is assumed to be weakened by HIPEC treatment, was questioned (5,7). It was thought that sildenafil would increase anastomotic blood flow by providing vascular vasodilation and increase anastomotic strength under HIPEC treatment by reducing microangiopathic damage due to hyperthermia and chemotherapy agents combined with HIPEC treatment.

Material and methods

Ethical Approval and Animal Subjects

In the present study, 30 female Wistar-Albino rats with an average weight of 250-300 grams and aged 20-28 weeks, and no history of medical treatment or surgical procedure were used. GPower 3.1 software was used for sample size calculation. All necessary approval was obtained from the institutional ethical review board (Approval no: 2021/11-6), and the research procedures complied with established ethical standards to safeguard the well-being of the animals involved. The rats were divided into three main groups, each containing 10 rats, which were the study group and given sildenafil citrate the control group, and the sham group.

Housing and Animal Care

Throughout the entire experiment, The rats in the same study group were monitored in separate cages in groups of 4. The rat pellet was provided both before and after the surgical procedure, and water was supplied ad libitum. All animals were housed and fed under controlled conditions with a 12-hour light/12-hour dark cycle at a room temperature of 24°C.

Experimental Groups and Study Design

Group 1 (Study group): After bowel anastomosis, HIPEC containing mitomycin C was performed via the closed method. Sildenafil citrate (10 mg/kg) was given orally by gavage for three days.

Group 2 (Control group): After bowel anastomosis, HIPEC containing mitomycin C was performed via the closed method.

Group 3 (Sham group): Only bowel anastomosis was performed.

Surgical Procedure

After the midline incision in the abdomen was made, the colon was found and 1 cm of the colon was resected 3 cm proximal to the peritoneal reflection without disturbing the vascularization of the left colon. The proximal end and distal ends were sutured with 7.0 prolene suture as a single-layer inverting suture and end-to-end anastomosis was achieved. Mitomycin C was applied for HIPEC according to the methods of Molyneux et al. (8). The drainage catheters were removed. The abdomen was closed with 5.0 silk sutures over a double layer.

HIPEC Administration

Mitomycin C was prepared at a dose of 15 mg/m2 after dilution with 20 mg. Half of the dose was placed in 100 mL of physiological saline. The fluid, which was brought to a temperature of 43°C with a heater, was infused into the abdomen with the help of a subdiaphragmatic catheter. Fluid from the drainage catheter was collected. The collected perfusate was rewarmed and reinfused with the help of infusion through the subdiaphragmatic catheter. Processing was continued for 30 minutes. The remaining dose was placed in two parts in another 100 mL of physiological saline. The same process was repeated twice for 30 min. The intraperitoneal temperature was measured during the procedure with a thermometer placed in the rectovesical area. The infusion temperature was changed to maintain the temperature between 40.5 and 41.5°C. After the procedure, the abdomen was opened and washed with physiological saline for 10 minutes. The drainage catheters were removed. The abdomen was closed with 5.0 silk sutures over a double layer. (Figure 1)

Sildenafil Administration

Sildenafil (10 mg/kg; dissolved in pH 4 water) was administered via orogastric gavage for three days, the first of which was administered at the 2nd postoperative hour.

Postoperative Evaluation and Sacrifice

Seven days after the procedure, the rats were

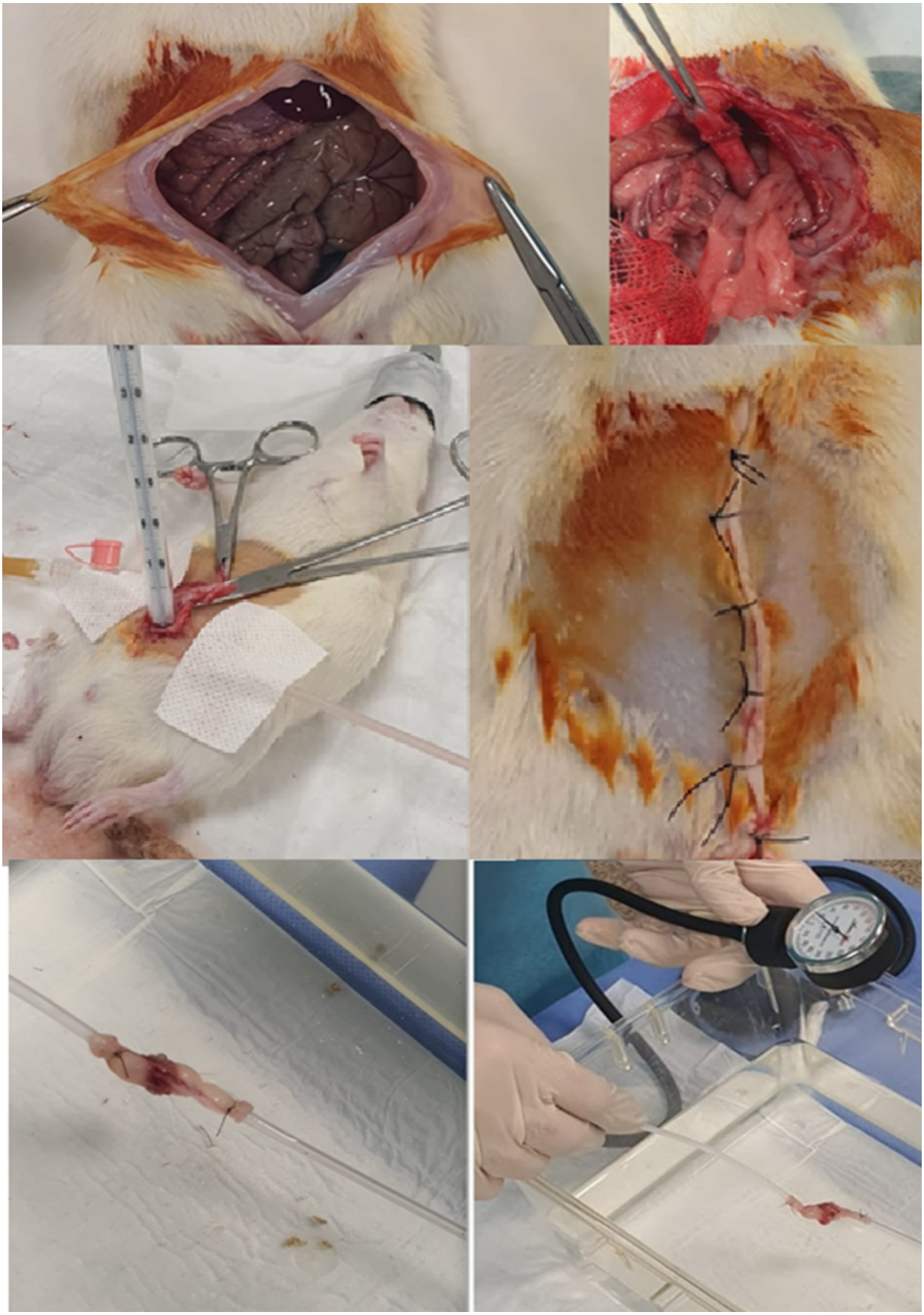

Figure 1. A) Rat abdomen undergoing laparotomy, **B)** Left colon after anastomosis, **C)** HIPEC process and peritoneal temperature measurement, **D)** Sutured abdomen with a silk suture, **E)** Burst pressure measuring setup, **F)** Burst pressure measuring with a sphygmomanometer

sacrificed by administering a high dose of anesthetic. The abdomen was opened and the anastomosis line was evaluated for adhesion. The anastomosis line was graded according to the adhesion around it. While the evaluation was carried out without the knowledge of the groups, data were collected by the researcher.

Measurement of Anastomotic Burst Pressure

The anastomotic loop was excised by extending 1 cm from the proximal and distal ends. The proximal end was threaded and ligated with an inflation device and the distal end was threaded and ligated with a sphygmomanometer. The loop was placed in a tub filled with water. The loop was inflated with air and pressure was measured with a sphygmomanometer. The integrity of the anastomosis was disrupted, air bubbles appeared and a sudden decrease in the sphygmomanometer was recorded by measuring the pressure. This pressure was accepted as the burst pressure.

Histopathological Examination

After the operation, the colon resection material of each rat was sampled by a pathologist, cassetteed, and paraffin blocked. The slides were prepared and stained with hematoxylin-eosin and Masson-Trichrome stains. Colon perforation, serosal inflammation, the presence of fibroblasts, mononuclear cells, and neovascularization were noted during the examination. Inflammatory granuloma and granulation tissue formation, fibrosis formation, inflammatory cell infiltration, and neovascularization were determined according to Ehrlich and Hunt's numerical scale modified by Phillips et al (9).

Statistical analysis

The Number Cruncher Statistical System (NCSS) (Utah, USA) program was used for statistical analysis. While evaluating the study data, descriptive statistical methods (mean, standard deviation, median, IQR, frequency, ratio) as well as the Shapiro-Wilk test and box plot graphics were used for assessing the compliance of the variables with a normal distribution. The Kruskal-Wallis test was used for the comparisons of the variables that were not normally distributed, and the Dunn test was used to determine whether the group was significantly different. The Fisher–Freeman Halton test was used to compare qualitative data. Significance was evaluated at the $p<0.05$ level.

Results

In the present study, there were two deaths in the study and control groups and one death in the sham group. New subjects were added to the study to complete the number instead of the number of dying subjects. One rat from the control group died on the 3rd postoperative day. In the sham group, two rats died on the 1st postoperative day and one rat died on the 2nd postoperative day. After sacrifice, the area around the anastomosis was evaluated for adhesion. There was a significant difference in adhesion between the sham group, sildenafil group (p=0.001), and control group (p=0.026) (Table 1).

Table 1. Perianastomotic adhesion

	Grade 0	Grade 1	Grade 2	Grade 3	Total	Median (IQR)
Sildenafil Group	0	2	3	5	10	2.5 (1-3)
Control Group	0	5	3	1	9	1 (1-3)
Sham Group	3	4	0	0	7	0 (0-1)
p						0.001**
Post hoc						$P_{1\&3}$=0.001** $P_{2\&3}$=0.026*

Kruskal Wallis test & post hoc Dunn test, *p<0.0, **p<0.01, IQR: 25%-75%

Anastomotic burst pressures were measured one by one. For five rats in the sildenafil group and four rats in the control group, measurements could not be performed because of point perforation or full-thickness separation. When the measured animals were evaluated, there was no significant difference among the three groups (p>0.05) (Table 2).

Table 2. Anastomosis Bursting Pressure

	Mean±SD	Median (IQR)	p
Sildenafil Group	160±23.45	150 (145-180)	
Control Group	150±8.16	150 (142.5-157.5)	**0.648**
Sham Group	179.68±71.61	200(125-250)	

Kruskal Wallis test, IQR: 25%-75%, SD: Standard deviation

Inflammatory granuloma and granulation tissue formation were compared between the groups. The inflammatory cell grades in the sham group were significantly lower than those in the sildenafil group (p=0.025) and control group (p=0,006) (Table 3).,

Table 3. Formation of inflammatory granuloma and granulation tissue

	Sildenafil Group	Control Group	Sham Group	p
Fibroblastic Proliferation				
Minimum	0	0	0	
Mild	1	4	4	
Moderate	4	5	1	
Intense	5	0	2	
Median (IQR)	3.5 (3-4)	3 (2-3)	2 (2-4)	0.025*
			Post Hoc	$P_{1\&2}$=0.003** $P_{1\&3}$=0.042* $P_{2\&3}$=0.878
Fibrosis formation				
Minimum	1	6	1	
Mild	3	3	5	
Moderate	6	0	1	
Intense	0	0	0	
Median (IQR)	3 (2-3)	1 (1-2)	2 (2-2)	0.000**
			Post Hoc	$P_{1\&2}$=0.001** $P_{1\&3}$=0.031* $P_{2\&3}$=0.001**
Giant cells				
Minimum	1	8	6	
Mild	8	1	1	
Moderate	1	0	0	
Intense	0	0	0	
Median (IQR)	2 (2-2)	1 (1-1)	1 (1-1)	0.001**
			Post Hoc	$P_{1\&2}$=0.001** $P_{1\&3}$=0.099 $P_{2\&3}$=0.006**
Neovascularization				
Minimum	1	8	6	
Mild	8	1	1	
Moderate	1	0	0	
Intense	0	0	0	
Median (IQR)	2 (2-2)	1 (1-1)	1 (1-1)	0.001**
			Post Hoc	$P_{1\&2}$=0.001** $P_{1\&3}$=0.099 $P_{2\&3}$=0.770

Kruskal Wallis test & post hoc Dunn test, *p<0.05, **p<0.01

When fibrosis formation was examined, fibrosis formation was significantly greater in the sildenafil group than in the control group and sham group (p=0.001; p=0.031). Fibrosis formation was significantly lower in the control group than in the sham group (p=0.001). Analysis of inflammatory infiltration revealed that the inflammatory infiltration in the sham group was significantly lower than that in the sildenafil group (p=0.002) and the control group (p=0.001).

Anastomotic wound inflammatory cell infiltration was compared between the groups. The values in the sham group were significantly lower than those in the sildenafil group (p=0.037) and the control group (p=0.001).

The histiocyte infiltration grade in the control group was significantly lower than that in the sildenafil group (p=0.001) and the sham group (p=0.006) (Table 4).

Table 4. Anastomotic inflammatory cell infiltration

	Sildenafil Group	Control Group	Sham Group	P
Histiocyte Infiltration				
Minimum	0	1	0	
Mild	4	8	5	
Moderate	6	0	2	
Intense	0	0	0	
Median (IQR)	3 (2-3)	2 (2-2)	2 (2-3)	0.001**

Kruskal Wallis test & post hoc Dunn test, *p<0.05, **p<0.01

In terms of giant cells, the histiocyte infiltration grades of the control group were found to be significantly lower than those of the sildenafil group (p=0.001).

Upon examining the neovascularization grades, no significant difference was observed between the sildenafil group and the control group (p=0.408).

Discussion

In colorectal cancers with peritoneal involvement, HIPEC is applied as a treatment in suitable patients (10,11). It has been shown that HIPEC application increases colorectal anastomotic leakage (12). There are few studies in the literature showing that sildenafil application increases the strength of colon anastomosis (5,13,14).

In our study, the death of five rats was observed during surgical intervention. These deaths were thought to be related to the effects of anesthesia. Replacement rats were included in the study to compensate for these losses. Additionally, four rat deaths were recorded during the follow-up period. These deaths were attributed to the effects of chemotherapy or a possible anastomotic leak.

Anastomotic leakage after HIPEC is a clinically important condition. In a study, rectal anastomotic leakage was observed in nine (22%) of 41 patients not undergoing the diverting ileostomy, and the mortality rate within 90 days was 7.1%(15). In another study, the rate of enteric fistula and leakage was 10.5% (16). Therefore, increasing the anastomotic strength and reducing the possibility of leakage without an invasive procedure such as a protective ileostomy are important in terms of clinical improvement and overall cost. Oral and topical agents are being used to prevent anastomotic leakage. For example, studies have shown that platelet-rich plasma applied topically to the anastomosis in rats treated with 5-fluorouracil and

HIPEC strengthens tissue healing (17,18). Sildenafil was used similarly in our study. In the rat model, the effects of sildenafil citrate on the physical resistance and histopathology of the anastomosis, which is assumed to be weakened by HIPEC, were examined.

There were no drug-related side effects or immune reactions throughout the study. In the present study, there were two deaths in the study and control groups and one death in the sham group. New subjects were added to the study to complete the number instead of the number of dying subjects. One rat from the control group died on the 3rd postoperative day. In the sham group, two rats died on the 1st postoperative day, and one rat died on the 2nd postoperative day. Intraoperative deaths were thought to be due to anesthesia-related complications, and postoperative deaths were thought to be due to sepsis. The limited number of rats used was a limitation of our study since the minimal number of rats recommended by the power analysis results was used.

In our study, there was no significant difference between the sildenafil group and the control group in terms of intra-abdominal adhesion. There was a significant difference between the Sham group and both groups. It has been shown in the literature that intraperitoneal chemotherapy causes adhesion (19). The difference with the Sham group is also in line with these results. In a study conducted in the rat anastomosis model in 2008, it was observed that intra-abdominal adhesions were significantly less in rats administered intraperitoneal sildenafil in the exploration performed on the 7th postoperative day (20). Contrary to oral administration in our study, intraperitoneal administration was performed. Although the dose of 8 mg/kg sildenafil given intraperitoneally during the operation was less than the daily dose of 10 mg/kg sildenafil given in our study, it was thought that it may have provided a higher effect in terms of bioavailability. Burst pressure could not be measured effectively in five rats in the sildenafil group and four rats in the control group. Anastomotic leakage occurred in nine rats that underwent HIPEC There was no difference in the number of rats that could be measured between the sildenafil group and the control group. According to various publications in the literature, sildenafil has positive effects on anastomotic burst pressure (13, 20). The reason why no difference was observed in our study is that the negative effect of HIPEC on anastomosis outweighs the effect of sildenafil. There was no significant difference in burst pressure between the sham group and the sildenafil and control groups. Since the burst pressure of the rats could not be measured during the statistical analysis, it was thought that there was no significant difference. In addition, meaningful results can be found in a study by using a larger sample of rats.

When the inflammatory granuloma and granulation tissue formation were examined, significant differences were observed between the sham group and the sildenafil and control groups in terms of the presence of inflammatory cells, and a more intense inflammatory response was observed in the HIPEC-treated rats. In terms of neovascularization, a significant difference was observed between the sham group and the control group, while a statistically insignificant difference was observed between the sham group and the sildenafil group. There was a significant difference between the sildenafil group and the control group in terms of fibroblastic proliferation and fibrosis formation. In a study conducted in canine open wounds in 2002, it was stated that fibroblastic proliferation increased in response to sildenafil and this change accelerated wound healing (21). Although sildenafil has been shown to reduce pulmonary fibrosis, it accelerates wound healing by increasing epithelial fibrosis during wound healing (22).

In our study, no significant difference was observed between the sildenafil group and the other groups in terms of neutrophil or lymphocyte infiltration or anastomotic inflammatory infiltration and neovascularization. While there was a significant difference between the sildenafil group and the control group in terms of histiocytes, a significant difference was observed between the sildenafil group and both groups in terms of giant cells. Giant cells and histiocytes play important roles in the granulation that occurs during wound healing. Consequently, sildenafil is expected to increase granulation.

In the meta-analysis of studies on anastomosis resistance, positive effects of many agents on anastomosis were observed. In addition, agents whose effectiveness has been proven in many studies have not been proven to have a significant effect (23-27). In our study, sildenafil increased fibrosis and granulation. However, there was no difference in burst pressure or adhesion, as were the differences in the agents used in other studies.

Study Limitations

A prominent limitation of this study is the lack of compatibility between the animal model and the

human model. When extrapolating chemical dosages from humans to rodents, an appropriate dosage cannot be established. Additionally, the limited similarity of wound healing between rodents and humans restricts the applicability of findings. Beyond these concerns, animal sampling may not be sufficient for producing statistically meaningful results.

Conclusion

On colon anastomosis performed together with HIPEC application, histopathologically positive effects of sildenafil were observed. The burst pressure of the colon anastomosis was not significantly different.

Disclosure Statement: The authors declare that they have no relevant or material financial interests that relate to the research described in this paper.

Statements and Declarations

1. Conflict of Interest Statement: The authors declare that they have no conflicts of interest regarding the publication of this paper.

2. Funding Statement: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

3. Ethical Approval: This research adhered to the ethical standards outlined in "The Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH), ensuring the appropriate care and use of animals. Additionally, international, national, and institutional guidelines relevant to the ethical treatment of animals in research were strictly followed. The study was conducted under the principles of "The International Guiding Principles for Biomedical Research Involving Animals." All necessary approval was obtained from the institutional ethical review board, and the research procedures complied with established ethical standards to safeguard the well-being of the animals involved.

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