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THE EFFECT OF CALCIUM DOBESILATE ON THE PREVENTION OF INTRAABDOMINAL ADHESIONS: AN EXPERIMENTAL STUDY

KALSİYUM DOBESİLAT'IN İNTRAABDOMİNAL ADEZYON ÖNLEYİCİ ETKİSİ: DENEYSEL ÇALIŞMA

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ABSTRACT

AIM: It was aimed to demonstrate the efficacy of Calcium Dobesilate (Ca-Dob) in preventing postoperative intra-abdominal adhesion formation in an experimental cecal abrasion model.

MATERIALS AND METHODS: Thirty female Wistar Albino rats used in the study were randomized into 3 groups. Laparotomy was performed in the sham group, the cecum was removed from the abdomen and replaced without any further processing. In the control group, after cecal abrasion and peritoneal resection no processing was applied. In the Ca-Dob group, abdomen was closed after cecal abrasion and peritoneal resection, then 100 mg/kg/day Ca-Dob was administered orogastrically for 21 days only this group. All rats were sacrificed on 21st day. The adhesions were evaluated. Tissue samples taken from the peritoneum and intestines were sent for histopathological examination to determine the degree of inflammation and fibrosis. Tissue and blood samples were taken for biochemical analysis.

RESULTS: Statistically, inflammation, microscopic adhesions and fibrosis scores were found to be significantly lower in the Ca-Dob administered rats compared to the control group ($p < 0.05$). Tissue Malondialdehyde (MDA), Fluorescent Oxidation Products (FOP) and Total Oxidation Status (TOS) values were found to be significantly lower statistically compared to the control group ($p = 0.001$). Tissue Total Sulfhydryl (Total SH) values were found to be statistically significantly higher ($p < 0.05$) in the sham group compared with the control group. Finally; serum MDA and serum TOS values in the Ca-Dob group, was statistically significantly lower ($p < 0.05$) compared to control group.

CONCLUSION: Ca-Dob was found to be efficacious in preventing the formation of adhesions. In addition to the demonstrated anti-inflammatory effect histopathologically, the effect of antioxidant effect demonstrated biochemically was concluded to participate to the adhesion preventive efficacy of Ca-Dob. Nevertheless, there is a need for further studies to assess the precise mechanism of the preventing of abdominal adhesions of Ca-Dob.

Keywords: *Calcium Dobesilate, Anti-inflammatory, Antioxidant, Adhesion, Experimental*

ÖZET

AMAÇ: Kalsiyum Dobesilat'ın (Ca-Dob) postoperatif intraabdominal adezyon oluşumunu önlemedeki etkinliğini deneysel çekal abrazyon modelinde göstermeyi amaçladık.

GEREÇ VE YÖNTEMLER: Çalışmada kullanılan 30 adet Wistar Albino dişi rat randomize olarak 3 gruba ayrıldı. Sham grubuna laparotomi yapıldı, çekum batın dışına alındıktan sonra herhangi bir işlem yapılmadan batına konuldu. Kontrol grubuna çekal abrazyon ve periton rezeksiyonu sonrası herhangi bir işlem yapılmadı. Ca-Dob grubuna çekal abrazyon ve periton rezeksiyonu yapıldıktan sonra batın kapatıldı, sadece bu gruba 21 gün boyunca 100 mg/kg/gün dozunda orogastrik yolla Ca-Dob verildi. Tüm ratlar postoperatif 21. gün sakrifiye edildi. Adezyon değerlendirmesi yapıldı. Periton ve barsaktan alınan doku örnekleri inflamasyon ve fibrozis derecelerini belirlemek için histopatolojik incelemeye gönderildi. Ayrıca, biyokimyasal analiz için doku ve kan örnekleri alındı.

BULGULAR: Ca-Dob uygulanan sıçanlarda inflamasyon, makroskopik adezyon ve fibrozis skorlarının kontrol grubuna göre istatistiksel olarak anlamlı derecede düşük olduğu saptandı ($p<0.05$).Yine, Ca- Dob grubunda doku Malondialdehit (MDA), doku Floresans Oksidasyon Ürünleri (FOÜ) ve doku Toplam Oksidan Durum (TOD) değerlerinin kontrol grubuna göre istatistiksel olarak anlamlı derecede düşük olduğu görüldü ($p=0.001$). Ayrıca sham grubundaki doku total serbest sülfidril grupları (Total SH) değerlerinin, kontrol grubuna göre istatistiksel olarak anlamlı derecede yüksek olduğu saptandı ($p<0.05$). Son olarak; Ca- Dob grubunda serum MDA ve serum TOD değerlerinin, kontrol grubuna göre istatistiksel olarak anlamlı derecede düşük olduğu görüldü ($p<0.05$).

SONUÇ: Ca-Dob'ın çekal abrazyon modelinde adezyon oluşumunu engellemede etkin olduğunu tespit ettik. Histopatolojik olarak gösterilen antiinflamatuar etkinin yanı sıra, biyokimyasal olarak saptanan antioksidan etkinin, Ca-Dob'ın adezyon önleyici etkinliğinde rol oynadığı sonucuna varılmıştır. Bununla birlikte, Ca-Dob'ın karın adezyonlarını önlemesinin kesin mekanizmasını değerlendirmek için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: *Kalsiyum Dobesilat, Antiinflamatuar, Antioksidan, Adezyon, Deneysel*

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This study was approved by the Ethics Committee of the Ministry of Health Ankara Training and Research Hospital

INTRODUCTION

Peritoneal adhesions are a result of peritoneal healing, causing significant morbidity and mortality. Postoperative peritoneal adhesions remain a serious problem in surgery for which there is no solution as yet. To date, a wide range of pharmacological agents and methods have been used in the prevention of postoperative intra-peritoneal adhesions and for prophylaxis. However, the conflicting results of these studies have rendered the prevention of postoperative intra-peritoneal adhesions an issue of importance in modern surgery (1).

Calcium Dobesilate (Ca-Dob) is a synthetic agent used in clinical practice for the treatment of chronic venous insufficiency, diabetic retinopathy, and of microangiopathies. Studies have also shown antioxidant, endothelial function regulation, and antiaggregant effects (2,3). Calcium Dobesilate is used in the treatment of venous diseases because of its known effects on improving the disorders of capillary function, reducing free oxygen radicals, increasing nitric oxide (NO) synthesis and its release, and preventing desquamation of endothelial cells (4,5).

In this study, it was aimed to examine the antioxidant effect of Calcium Dobesilate administered orally, in the potential prevention of intra-abdominal adhesion formation in a rat cecal abrasion model.

MATERIAL AND METHODS

Animals

This study was approved by the Ethics Committee of the Ministry of Health Ankara Training and Research Hospital. A total of 30 Wistar Albino female rats, each weighing 225 ± 25 gr. were randomly separated into 3 groups of 10 and kept in cages at 21 ± 2°C, and in a 12 hour light/dark cycle.

Surgical Procedure

Surgical intervention was performed under sterile conditions by the same team. All the rats were fasted for 12 hours before the intervention. No rats were administered any enteral and/or parenteral antibiotics during the study. Anesthesia was administered of intramuscular 30 mg/kg ketamine hydrochloride (Ketalar ®; Parke-Davis, Istanbul, Turkey) and 5 mg/kg xylazine (Rompun ®; Bayer, Istanbul, Turkey). Abdominal entry was made with a midline incision in all rats. After this intervention, the following procedures were applied to the groups:

Group 1 (Sham): The cecum was removed from the abdomen then replaced without any other procedure.
Group 2 (Control): Cecal abrasions and peritoneal resections were performed with no further treatment.
Group 3 (Calcium Dobesilate group): Cecal abrasions and peritoneal resections were performed then 100 mg/kg/day Calcium Dobesilate was administered orogastrically for 21 days.

Cecal abrasions were formed by applying sterile gauzes to the anterior wall until subserous hemorrhage occurred. Peritoneum resections were performed by extraction of pieces of peritoneum with a diameter of 1 cm, in the area of the peritoneum facing where the cecal abrasions were applied. On completion of the interventions, the abdomens of the rats in all 3 groups were closed using continuous fascia and skin 3/0 silk sutures.

Throughout the duration of the experiment, all rats received a standard rat diet. On the 21st postoperative day, all the rats were sacrificed using high-dose ketamine anesthesia. The abdomens of the rats were opened with a U-shaped incision extending from the pelvis to the bilateral costal arches. Intraperitoneal adhesions were scored according to the Leach et al.'s clinical adhesion scoring systems. Macroscopic adhesion scores were performed by a group of surgeons, blinded to the study groups of the animals using a method based on expansion, appearance, and resistance to applied forces **(Table 1)** (6).

To investigate the mechanism of the effect, tissue samples taken from the peritoneum and intestines were sent for histopathological examination to determine the degree of inflammation and fibrosis. Tissue and blood samples were taken for biochemical analysis.

Histopathological Evaluation

The rat intestinal tissue samples, 3x2 cm in dimensions were fixed in 10% formaldehyde solution for 1 day, and then embedded in paraffin after ethanol graded dehydration (50%, 75%, 96%, and 100%) and xylene rendered transparency phases. Tissue sections were examined following staining by Hematoxylin & Eosin (H & E) and Mason Trichrome. Histopathological examination was performed using OLYMPUS brand, BX51TF model, x4, x10, x20, x40 magnification. The presence of any inflammation in the H&E stained slices, and the presence of any fibrosis in the Mason-Trichrome stained ones were

Table 1. Macroscopic adhesion scoring

Score	**Expansion** (Adhesion/incision)	**Appearance**	**Resistance**
0	Absent	Absent	Absent
1	Less than 25%	Tulle, transparent, avascular	Easy detachment
2	25-50%	Opaque, translucent, avascular	Detached by traction
3	50-75%	Opaque, translucent, capillary	Detached by sharp dissection
4	more than 75%	Opaque, thick veins are present	

*Adhesion score is equal to the sum of all scores attributed on each part. The highest possible score is 11.

evaluated by pathologists, blinded to the study groups. The evaluation was performed using the semiquantitative histopathological scoring system: Fibrosis scores; 0: Absent, 1: Mild, weak, 2: Moderate intensity,3: Severe, intense. Inflammation scores; 0: Absent, 1: Giant cells, lymphocytes and plasma cells, 2: Giant cells, plasma cells, eosinophils and neutrophils, 3: A large number of inflammatory cells, formation of microabcess (7-9).

Biochemical Analysis

Tissue homogenates for biochemical examination were prepared as follows: Tissue homogenates of 1/10 (w/v) were prepared in 50 mM PBS in iced water with a Heidolph DIAX 900 homogenisator. Malondialdehyde (MDA), fluorescent oxidation products (FOP) and total sulfhydryl (Total SH) groups were examined in the homogenate, and Total Oxidation Status (TOS) was examined in the supernatant. The supernatant was obtained by centrifuging the tissue homogenates at + 4 C ° and 15.000 g for 10 minutes (10).

MDA measurement was performed using the Ohkawa et al method based on the principle of measurement of the optical density of the color, formed by the MDA combined with thiobarbituric acid in the acidic media, at 532 nm. 0.2 ml 8.1% sodium dodecyl sulfate, 1.5ml 20% acetic acid with a pH of 3.5, and 1.5 ml 0.8% thiobarbituric acid solution were added to 0.5 ml plasma and the mixture was heated at 95° C for 60 minutes. After cooling, it was centrifuged at 4000 revolution speed for 10 minutes. The top layer absorbance was measured at 532 nm. As a standard, the MDA amount in the sample was calculated with the calibration graph using 1, 1.3, 3-tetraethoxypropane. Results were defined as nmol/ml for the plasma, and nmol/g for the tissues (11).

The TOS measurement was performed using the calorimetric method based on the cumulative oxidation of the molecules in the sample from ferrous ion to ferric ion. The results were expressed as μmol H2O2 Equivalent/ L (12).

Statistical Analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 15.0 for Windows software (SPSS Inc, Chicago, IL). All variables were normally distributed about the mean. Data were presented as mean ± standard deviation (SD). Differences between the groups were evaluated with one-way analysis of variance (ANOVA) or Kruskal-Wallis variance analysis, whichever was appropriate. When the p values from the variance analysis were statistically significant, the Tukey honestly significant difference (HSD) or Mann- Whitney U multiple comparison tests were used to determine which group was different from the others. A value of $p<0.05$ was considered to be statistically significant.

RESULTS

A total of 6 rats died on postoperative day 1; 3 rats in the sham group, 1 rat in the control group, and 2 rats in the Calcium Dobesilate group. All rats were sacrificed on the 21st post-operative day by high dose ketamine anesthesia.

Macroscopic Adhesion Scores

Macroscopic mean adhesion scores in Ca-Dob applied rats (3.25 ± 0.84) and in the sham group (1.28 ±0.61) were statistically significantly lower ($p<0.05$ for both groups) compared to the control group (6.33±1.80). The difference between the sham and the Ca-Dob group was not statistically significant ($p > 0.05$).

Histopathological Results

The mean histopathological scores of the groups are presented in **Table 2.** Inflammation scores were statistically significantly lower in the Ca-Dob group compared to the control group ($p <0.05$). No statistically significant difference was observed between the sham group and Ca-Dob group ($p > 0.05$).

Table 2. The mean histopathological scores of the groups

	Fibrosis	Inflammation
Sham (n=7)	**0.14 ±0.06**	**0.71 ±0.33**
Control (n=9)	**1.44 ±0.11[a, b]**	**2.67 ±0.48[a, b]**
Ca-Dob (n=8)	**0.25 ±0.08**	**1.00 ±0.024**

[a]:Significant difference has been observed between the sham group and the control group: $p<0.05$

[b]:Significant difference has been observed between the control group and the Ca-Dob group: $p<0.05$

Fibrosis scores were found to be statistically significantly lower in the Calcium Dobesilate administered group compared to the control group ($p<0.05$). There was no statistically significant difference between the sham group and the Ca-Dob group ($p > 0.05$).

The histopathological images are presented in **Figures 1 and 2.**

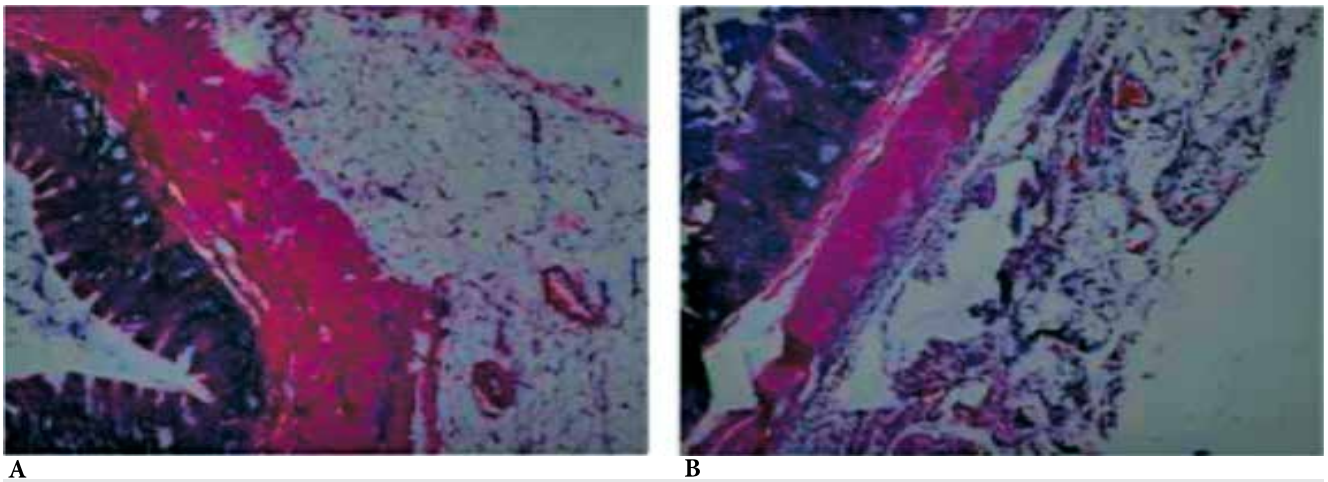
Biochemical Results

All the groups were evaluated in respect of tissue MDA, FOP, total SH, and serum MDA and TOS values **(Table 3).**

When all the groups were evaluated in terms of tissue MDA, the values were statistically significantly lower in the Ca-Dob and the sham group compared to the control group ($p<0.05$).

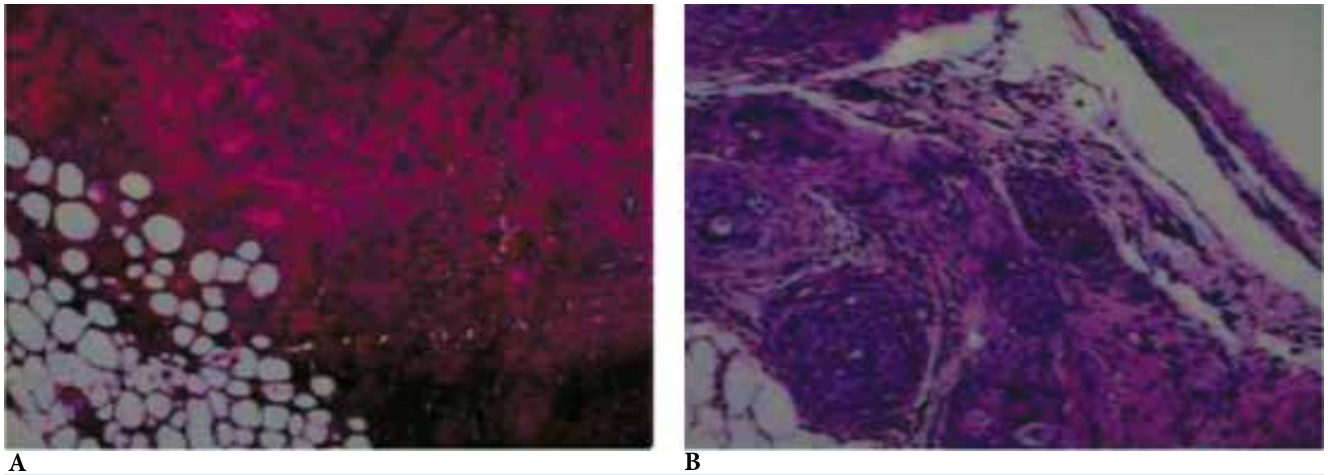
Tissue FOP values were statistically significantly lower in the Ca-Dob and in the sham group compared to the control group ($p<0.05$). The values were statistically significantly lower in the sham group compared to the Ca-Dob group ($p<0.05$).

Tissue Total SH values were evaluated in all groups and found to be statistically significantly higher in the sham group compared to the control group ($p<0.05$). No statistically significant results were observed between the Ca-Dob and control group, and between the sham and Ca-Dob group ($p>0.05$).



A B

Figure 1. A. Sham group **B.** In the Ca-Dob group, inflammation and fibrosis on the serosal surface of the colon wall was observed to be less or not present. (Hematoxylin & Eosin stain, H & E) (x100)



A B

Figure 2. A. In the control group, intense inflammation loci were observed adjacent to theserosal surface on the colon wall (x100) **B**. The cells forming the inflammation consist of foreign body-type multinucleated giant cells, eosinophilic leukocytes, lymphocytes, and plasma cells (x200)

Table 3. The mean values of oxidative stress parameters

	Sham	Control	Ca-Dob
Tissue MDA (nmol/g protein)	16.85 ± 4.66	119.27±27.21[a,b]	30.03 ± 8.42
Tissue FOP (RFU/g protein)	60.42±14.16	272.33±68.43[a,b]	100.62±37.12[c]
Tissue Total SH (umol/g protein)	42.28 ± 15.66	18.00 ± 5.17[a]	27.62±6.44
Serum MDA (nmol/L)	42.00±10.51	115.55±24.32[a,b]	57.12±12.14[c]
Tissue TOS (nmol H_2O_2 equivalant/g protein)	1358.42±307.86	2624.00 ± 531.81[a,b]	1779.87 ± 300.41[c]
Serum TOS (umol H_2O_2 equivalant/L)	18.25±3.14	43.19±14.70[a,b]	25.74±6.25[c]

[a]:Significant difference has been observed between the sham group and the control group: p<0.05
[b]:Significant difference has been observed between the control group and the Ca-Dob group: p<0.05
[c]:Significant difference has been observed between the sham group and the Ca-Dob group: p<0.05

All the groups were evaluated in terms of tissue TOS and the results were statistically significantly lower in the sham group compared to the control group (p<0.05). The values were observed to be statistically significantly lower in the Ca- Dob group compared to the control group (p<0.05). The values were statistically significantly lower in the sham group compared to the Ca-Dob group (p<0.05).

When all the groups were evaluated in terms of Serum MDA, the values in the sham group were found to be statistically significantly lower compared to the control group (p<0.05). The values were observed to be statistically significantly lower in the Ca-Dob group compared to the control group (p<0.05). The values were statistically significantly lower in the sham group compared to the Ca- Dob group (p<0.05).

When the groups were evaluated in terms of Serum TOS, the values were statistically significantly lower in the sham group compared to the control group ($p<0.05$). The values were observed to be statistically significantly lower in the Ca-Dob group compared to the control group ($p<0.05$). The values were statistically significantly lower in the sham group compared to the Ca-Dob group ($p<0.05$).

DISCUSSION

The formation of postoperative adhesions is accepted as a part of peritoneal healing. The main causes of postoperative adhesions are reported to be peritoneal trauma, tissue ischemia, infections and foreign bodies (13).

Adhesions render re-laparotomies difficult and increase the rate of complications. Similarly, adhesions hamper laparoscopic surgery and sometimes make it impossible to perform. Bowel injuries, which occur during the detachment of adhesions are serious complications, seen at a rate of 20% (14). In addition to causing a prolonged duration for adhesiolysis, anesthesia, and operation, they constitute probable risk factors for blood loss, organ damage, fistula formation, and bowel resection (15).

Peritoneal wound healing differs from skin wound healing in the phases of both epithelialization and fibrin deposition. Unlike skin wounds that heal from the edges, repair of peritoneal defects starts from the underlying mesenchymal layer. Consequently, both large and small peritoneal defects heal relatively quickly (16).

Precautions to be taken to minimize adhesion formation include the application of delicate and appropriate surgery methods, avoiding excessive manipulation of tissues, providing adequate hemostasis, not leaving ischemic and necrotic tissues in the abdomen, preventing desiccation of the intestines, fighting against intra-abdominal infections, using the least reactive suture material, and keeping any foreign substances such as powder and starch away from the abdomen. However, even in situations where all these precautions have been applied meticulously, the formation of adhesions cannot always be prevented (1,17,18). In addition, the use of laparoscopic methods to minimize peritoneal trauma during operations has not completely prevented adhesion formation (19).

Local intraperitoneal oxidative stress contributes to the formation of peritoneal adhesions. Oxidative stress of the peritoneum increases the formation of adhesions by not only disturbing the mesothelial fibrinolytic activity, but also by increasing angiogenic factors, which cause over-healing of the peritoneum (20).

Free oxygen radical scavengers have been shown to reduce the formation of adhesions significantly in ileal ischemia-reperfusion and experimental endometriosis models. Besides the cytotoxic effects of free oxygen radicals on mesothelial cells, it has been demonstrated that they induce apoptosis. These mechanisms lead to progressive mesothelial damage during surgery and an increase in postoperative adhesions. In addition to causing mesothelial cell death, free oxygen radicals have a negative effect on the fibrinolytic properties of the mesothelium. Free oxygen radicals inhibit fibrinolysis by increasing plasminogen activator- inhibitor release from mesothelial cells (20).

In the targeting of the phases of the adhesion formation mechanism, several agents have been tried such as steroids, non-steroidal anti-inflammatory drugs, antihistamines, heparin, methylene blue, aprotinin, urokinase, melatonin, recombinant tissue plasminogen activators, dextran, vitamin E or carboxymethyl cellulose to act as a barrier, hyaluronic acid, amniotic fluid, honey, and fibrin glue to reduce the initial inflammatory response, to prevent fibrin formation, to increase fibrinolysis, and to prevent collagen storage (21-24).

The primary objective of studies on the prevention of postoperative adhesions has been to reduce or eliminate adhesions without disturbing the physiological healing. Although many studies have been conducted on the causes and prevention of adhesions, no methods or drugs have yet been developed to prevent postoperative adhesion formation (1).

Calcium Dobesilate is a synthetic sulfobenzene derivative and an angioprotective agent, which can be administered orally or intravenously. In clinical practice, it is used in the treatment of chronic venous insufficiency, diabetic retinopathy and microangiopathies. In addition, studies have demonstrated its effects on antioxidation, endothelial function regulation, and anti-aggregation (2,3). The effect on the endothelium is seen through the increase in endothelial NO synthesis. With this antioxidant effect, it reduces capillary permeability, increases lymphatic drainage, and decreases blood viscosity. Experimental studies have demonstrated that it increased nitric oxide synthase activity (4,5). Calcium Dobesilate conducts its anti-aggregant activity on cyclic adenosine monophosphate (cAMP) by activating the adenylate cyclase enzyme. It also exhibits an antioxidant effect by eliminating the free oxygen radicals which activate endothelial damage (25-27).

In an investigation of the effect of Calcium Dobesilate on intestinal ischemia, reperfusion injury, and the antioxidant system in rats, Seker et al. (28) identified that Calcium Dobesilate reduced the serum and tissue oxidative stress index by increasing the total antioxidant capacity. In addition, the histopathological analysis demonstrated that Calcium Dobesilate reduced tissue damage.

In a rat model study by Brunet et al. (27), Calcium Dobesilate was found to protect peritoneal vascularization by decreasing the permeability caused by free oxygen radicals. Furthermore, Calcium Dobesilate was reported to be protective against oxidative stress and inflammation in human varicose veins due to the antioxidant and anti-inflammatory effects. Garay et al. (29) stated that Calcium

Dobesilate could protect against diabetic endothelial dysfunction and reduced apoptosis in addition to antioxidant activity.

In the current study, postoperative adhesion development was seen to occur less in the Calcium Dobesilate group compared to the control group. In the histopathological evaluation of the tissues, Calcium Dobesilate was seen to have reduced the development of inflammation and fibrosis at statistically significant rates.

In addition, biochemical evaluations of tissue and serum enzyme activities demonstrated a significantly positive effect on the prevention of oxidative stress. It was concluded that this biochemically determined antioxidant effect resulted in the efficacy of Calcium Dobesilate in the prevention of adhesions.

CONCLUSION

The results of this study demonstrated that Calcium Dobesilate, which is a cheap and reliable molecule, administered at specified therapeutic doses and times, was effective in preventing inflammation and fibrosis, reduced oxidative stress, and ultimately decreased intraperitoneal adhesion formation macroscopically. Previous studies have also shown its antioxidant, endothelial function regulatory, and anti-aggregant effects. To the best of our knowledge, this is the first study in the literature that investigates the effect of Calcium Dobesilate on the prevention of experimental abdominal adhesions. Nevertheless, there is a need for further studies to assess the precise mechanism of the preventing of abdominal adhesions of Calcium Dobesilate.

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