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ORIGINAL ARTICLE / ÖZGÜN MAKALE

The comparison of alpha lipoic acid with methylprednisolone and sucralfate in subacute wound healing corrosive esophagus-induced rats: An experimental study

Koroziv özofagus oluşturulan sıçanlarda subakut yara iyileşmesinde alfa lipoik asidin metilprednizolon ve sukralfat ile karşılaştırılması: Deneysel çalışma

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ABSTRACT

Background: This study aims to compare methylprednisolone frequently used in the therapeutic practices of corrosive esophagus burns, sucralfate, a protective material of mucosal surfaces, and alpha lipoic acid, the most potent antioxidant in a rat model.

Methods: A total of 40 female Sprague-Dawley rats were used in this study. The rats were equally divided into control, alpha lipoic acid, methylprednisolone, and sucralfate groups (n=10). A corrosive esophagus burn was created by using 10% pH:12 sodium hydroxide. No treatment was applied to the control group, and each group was given their own treatment. The treatment was continued regularly until the eighth day, when they were sacrificed. The corrosive esophagus burn lines were removed and tissue sections were stained with hematoxylin and eosin.

Results: The difference in ulceration in the group treated with alpha lipoic acid was significant, compared to the other groups. The most excellent complete epithelialization and complete re-epithelialization were observed in the alpha lipoic acid group. The difference between the groups was significant, with complete re-epithelialization being the lowest in the control and methylprednisolone groups (42.9% and 12.5%, respectively) and the highest in the alpha lipoic acid group (77.8%). In terms of ulceration and re-epithelialization, comparable values were found in the alpha lipoic acid group. The main difference was that the inflammation levels in the sucralfate group were lower and more favorable than the other groups in this period. The glutathione level was significantly higher in the alpha lipoic acid group and decreased the tissue hydroxyproline level.

Conclusion: Alpha lipoic acid reduces esophageal ulceration, severity and prevalence of inflammation, severity and prevalence of fibrosis, decreases tissue damage by increasing blood glutathione level, and also reduces stricture in corrosive esophagus burns in rats.

Keywords: Alpha lipoic acid, corrosive esophagus, methylprednisolone, stricture, sucralfate.

ÖZ

Amaç: Bu çalışmada bir sıçan modelinde korozif özofagus yanıklarının tedavi uygulamasında sıklıkla kullanılan metilprednizolon, mukoza yüzeyinin koruyucu maddesi olan sukralfat ve en etkili antioksidan olan alfa lipoik asit karşılaştırıldı.

Çalışma planı: Bu çalışmada toplam 40 adet dişi Sprague-Dawley cinsi sıçan kullanıldı. Sıçanlar eşit olarak, kontrol, alfa lipoik asit, metilprednizolon ve sukralfat gruplarına ayrıldı (n=10). Gruplar %10'luk pH:12 sodyum hidroksit kullanılarak, korozif özofagus yanığı oluşturuldu. Kontrol grubuna tedavi uygulanmaz iken, her gruba kendi tedavileri verildi. Tedaviye sakrifiye edildikleri sekizinci güne kadar düzenli olarak devam edildi. Korozif özofagus yanık hatları çıkarıldı ve doku kesitleri hematoksilen ve eozin ile boyandı.

Bulgular: Alfa lipoik asit ile tedavi edilen grupta oluşan ülserasyon açısından görülen fark, diğer gruplar ile karşılaştırıldığında, anlamlı idi. En iyi tam epitelizasyon ve tam re-epitelizasyon alfa lipoik asit grubunda izlendi. Tam re-epitelizasyon kontrol ve methylprednisolone grubunda en az (sırasıyla, %42.9 ve %12.5), en iyi alfa lipoik asit grubunda (%77.8) olması ile gruplar arasındaki fark anlamlıydı. Ülserasyon ve re-epitelizasyon açısından alfa lipoik asit grubunda yakın değerler izlendi. En önemli fark, bu dönemde sukralfat grubundaki enflamasyon düzeylerinin diğer gruplara kıyasla daha düşük ve daha iyi olması idi. Alfa lipoik asit grubunda glutatyon düzeyinin anlamlı olarak yüksek olduğu ve doku hidroksiprolin düzeyini düşürdüğü belirlendi.

Sonuç: Alfa lipoik asit sıçanlarda özofagus ülserasyonunu, enflamasyonun şiddetini ve prevalansını, fibrozisin şiddetini ve prevalansını azaltır, kan glutatyon düzeyini yükselterek doku hasarını azaltır ve aynı zamanda korozif özofagus yanığında striktürü azaltır.

Anahtar sözcükler: Alfa lipoik asit, korozif özofagus, metilprednizolon, striktür, sükralfat.

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Accidentally or with the purpose of suicide, drinking corrosive substances, particularly alkali solutions, constitutes a severe health problem, since this may result in such severe health problems in esophagus as ulcer, perforation, and even death. Although antioxidant, immunosuppressive, and antiaggregant drugs, antibiotics, collagenous synthesis inhibitors, beta-aminopropionitrile acids, penicillamine, N-acetylcysteine, and ketotifen have been experimentally shown to prevent the development of stricture due to alkali, there are no clinical studies on this topic.[1-3] Esophagus burns caused by corrosive materials are considerable, since they are accompanied by serious complications.[4] Drinking strong corrosive materials, particularly alkalies, may result in acute perforation and death. However, among the patients surviving from the acute period, the development of stricture may give rise to problems.[5]

Corrosive esophagitis peaks between the ages of 1 and 5 among children and 20 and 30 in adults.[6] The risk of esophageal carcinoma is one thousand-times higher in population with damages caused by caustic, compared to normal individuals. Typically, squamous-cell carcinoma develops in the middle part of esophagus. Cancer develops within four to five decades after the caustic damage.[7,8]

Methylprednisolone (MP), which is frequently used in the treatment of corrosive esophagus, aims to prevent stricture with its effect on reducing neovascularization, collagen synthesis, contraction, oxidase activity, and inflammation. Sucralfate (SCF) acts as a barrier by forming a complex with the protein and fibrinogen layer on the ulcer, and has a cytoprotective effect and a reducing effect on the development of scar tissue. In the corrosive esophagus, oxidative damage occurs, starting from the mucosa and involving all layers. Therapeutic agents that reduce oxidative stress result in restoring mitochondrial function, combating disease, and improving quality of life. Alpha lipoic acid (ALA) is a powerful antioxidant that is both fat- and water-soluble, reduces oxidative stress, and improves the level of other antioxidants.

In the present study, we aimed to compare MP frequently used in the therapeutic practices of corrosive esophagus burns (CEBs), SCF, a protective material of mucosal surfaces, and ALA, the most potent antioxidant in rats.

MATERIALS AND METHODS

This study included a total of 40 female Sprague-Dawley rats with the weight of 162 to 225 g. The rats were divided into four groups including 10 rats in each group. Corrosive esophagus burns were created in all animals, and no treatment was performed for rats in Group 1. Alpha lipoic acid in Group 2, ALA 100 mg/kg/day was injected into the rats intraperitoneally on the same day (having been put into distilled water for intraperitoneal applications, dissolved with sodium hydroxide [NaOH] salt and treated with hydrochloric acid [HCl] to maintain a pH of 7.2 to 7.3, ALA became appropriate for intraperitoneal applications). In rats in Group 3, MP was injected intramuscularly (30 mg/kg/day), and Group 4 was treated with SCF via oral gavage (150 mg/kg/day). Experimental animals were kept hungry for 12 h and weighed. After performing anesthesia with a mixture of 100 mg/kg of ketamine HCl + 15 mg/kg 2% xylazine through subcutaneous injection, the rats were positioned on the table on their backs, and their four feet were fixed. Chemical esophagus burns were formed in light of the method described by Liu and Richardson[9] The sterilized abdominal region was covered with a sterile cloth, and laparotomy was applied to the rats (Figure 1a). After abdominal esophagus was asserted, the distal edge of the esophagus (the entrance to the stomach) was closed via a bulldog clamp (Figure 1b). At the second stage, a silicon urinary catheter (pediatric) of 6Fr was orally inserted until the region clamped with a bulldog. Afterwards, the cuff of catheter was pumped up with some air of 1.5 cc, and the region where an esophagus burn was formed (from the margin of the catheter and the cuff) was isolated. Then, 10% of NaOH, pH:12 was sent at enough amount to fill the closed distal esophagus segment with an injector.[10] After 90-sec-interval, the corrosive substance was drawn back into the injector, the esophagus was washed with distilled water, the clamp was opened, the catheter was taken out, and the abdomen was closed in accordance with the procedure (Figure 1c). The treatment was continued for eight days. All rats were sacrificed with anesthetics. Corrosive esophageal burns formed line removed for pathological study (Figure 1d).

The esophagus segments determined via 10% of formalin were shown through hematoxylin and eosin (H&E) and triple (MTC) dying. In the histopathological evaluation, ulceration, re-epithelialization, the severity and extensity of inflammation, the severity and extensity of fibrosis and the index of stenosis were investigated by scoring each in its group.

The level of glutathione (GSH) was measured using the enzyme-linked immunosorbent assay (ELISA) method using the Cayman's kit (Cayman Chemical Inc., MI, USA).

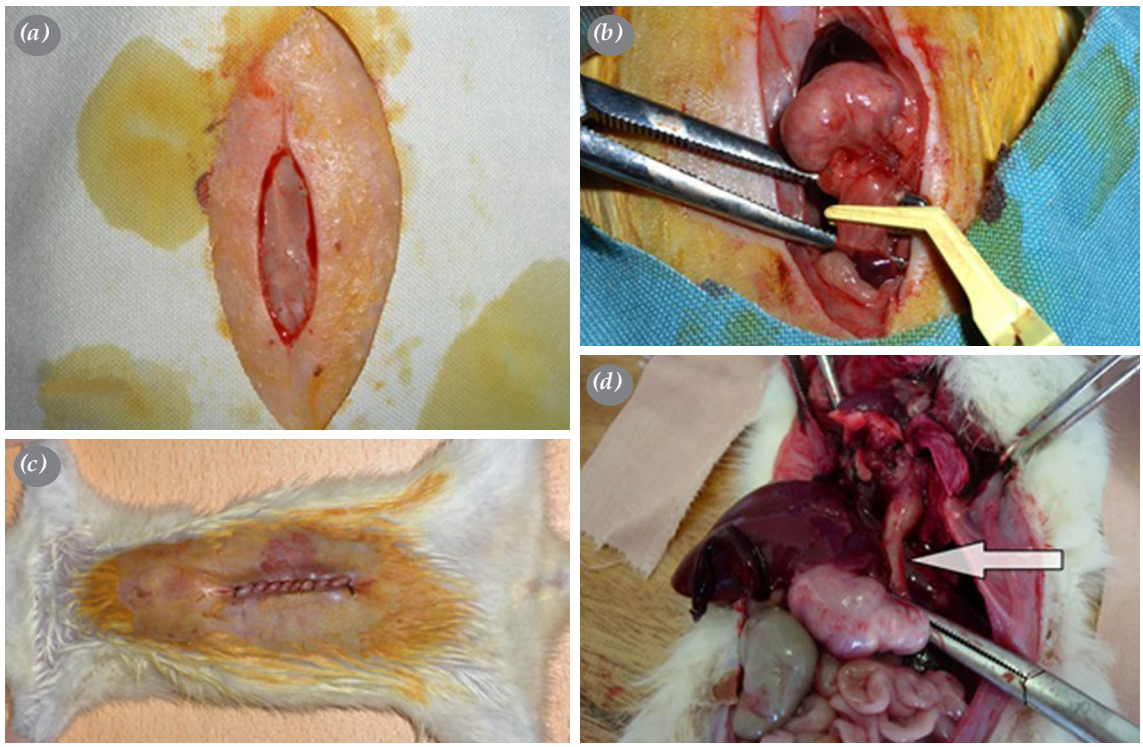

Figure 1. (a) Skin incision for laparotomy. **(b)** Distal esophagus and bulldog clamp closure. **(c)** Suturing the laparotomy incision. **(d)** Corrosive esophagus formed segment removed after sacrification, white arrow.

Statistical analysis

Statistical analysis was performed using the SPSS version 13.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean ± standard deviation (SD) or number and frequency, where applicable. In terms of weight changes, the groups were analyzed with the one-way analysis of variance (ANOVA) test. The comparison of groups was simultaneously performed via the post-hoc Tukey's honestly significant difference test of ANOVA. The chi-square test was used to analyze categorical variables. A p value of <0.05 was considered statistically significant.

RESULTS

The weights of all rats were measured before the surgical procedure and sacrification. In the comparison of groups, the fact that loss of weight was the least in the ALA group (mean: 6.1±3.4 g). Simultaneous comparison of the weight difference between the first and last weights of the groups revealed a statistically significant difference (p<0.05) (Table 1). The ulceration scores of the groups are shown in Table 2, indicating a statistically significant difference among the groups. When the percentages of groups were analyzed, the damage including submucosa and deep muscular layer or all the layers was found to be significantly higher in controls, compared to the other groups (p<0.05).

Within the groups treated, the level of improvement was higher in the ALA, MP and SCF groups, compared to controls. While no ulceration was observed in 66.7% (n=6) of ALA group, the incidence rates of ulceration in the MP and SCF groups were 25.0% (n=2) and 50.0% (n=4), respectively. Ulceration was present in all strata of the rats in controls. While Grade 2 (muscular mucosa) was mostly determined in SCF group, the grade was 3 in the ALA group and 2 in the MP and in control groups. Grade 4 (deep muscular layer or including all the layers) was mostly observed in the control group (n=2). Re-epithelialization was evaluated in the subacute period in the groups. Histopathological scoring of re-epithelialization is demonstrated in Table 3. Re-epithelialization histopathological scoring values were evaluated and a statistically significant difference was found (p<0.05). In the analysis of all groups, while no re-epithelization was seen in the controls (n=3, 42.9%) and MP group (n=1, 12.5%), incomplete epithelization was seen at most in controls (n=4, 57.1%) (Figure 2b, c), and at a lower amount, in the MP and SCF group (n=3, 37.5%, and n=3,

Table 1. Simultaneous difference between the initial and final weights comparison

	Mean difference	Standard error	*p*
Group 1			
Group 2	10.476	1.901	0.001
Group 3	4.518	1.952	0.119
Group 4	9.893	1.952	0.001
Group 2			
Group 1	-10.476	1.901	0.001
Group 3	-5.958	1.833	0.015
Group 4	-0.583	1.833	0.989
Group 3			
Group 1	-4.518	1.952	0.119
Group 2	-5.958	1.833	0.015
Group 4	5.375	1.886	0.038
Group 4			
Group 1	-9.893	1.952	0.001
Group 2	0.583	1.833	0.989
Group 3	-5.375	1.886	0.038

Table 2. Ulceration scoring

Grade	Ulceration localization
Grade 0 (Score=0)	None
Grade 1 (Score=1)	Only in epithelium
Grade 2 (Score=2)	Muscular mucosa
Grade 3 (Score=3)	Submucosa
Grade 4 (Score=4)	Deep muscular layer or whole layer

37.5%, respectively). The highest re-epithelization was observed in the ALA group with the rate of 77.8% (n=7), and complete re-epithelization was found to be 62.5% (n=5) in the SCF group (Figure 2d).

Inflammation severity and inflammation prevalence scoring was done (Table 3). Inflammation severity values were evaluated. Since Grade 0 was not detected in all of the groups, the difference was not considered statistically significant (p>0.05). When Grade 1 and Grade 2 scoring were analyzed according to their percentage distribution, inflammation was mild in 14.3% (n=1) and severe in 87.5% (n=6) of the control group. In the treated groups, the severity of inflammation was 75.0% (n=6) in the SCF group and 66.7% (n=6) in the ALA group. Considering the severity and extent of inflammation scoring, the severity of inflammation was 75.0% (n=6) in the SCF group and 66.7% (n=6) in the ALA group. Compared the groups in terms of distribution rates, the extensity of inflammation included all layers in controls (n=6, 85.7%) and less layers in the ALA group (n=3, 33.3%). When the ALA, MP and SCF groups were compared, the extensity of inflammation was found to be Grade 1 in the ALA group as 66.7% (n=6).

Table 3. Inflammation severity and inflammation prevalence scoring

	RS	ISS	IPS	FSC	FES
Grade 0 (Score=0)	None	None	None	None	None
Grade 1 (Score=1)	Incomplete	Light	Not retaining all layers	Light	Submucosal or focal
Grade 2 (Score=2)	Complete	Severe	Keeping all layers	Severe	Keeping all layers

RS: Reepithelialization scoring; ISS: Inflammation severity scoring; IPS: Inflammation prevalence scoring; FSC: Fibrosis severity scoring; FES: Fibrosis extent scoring.

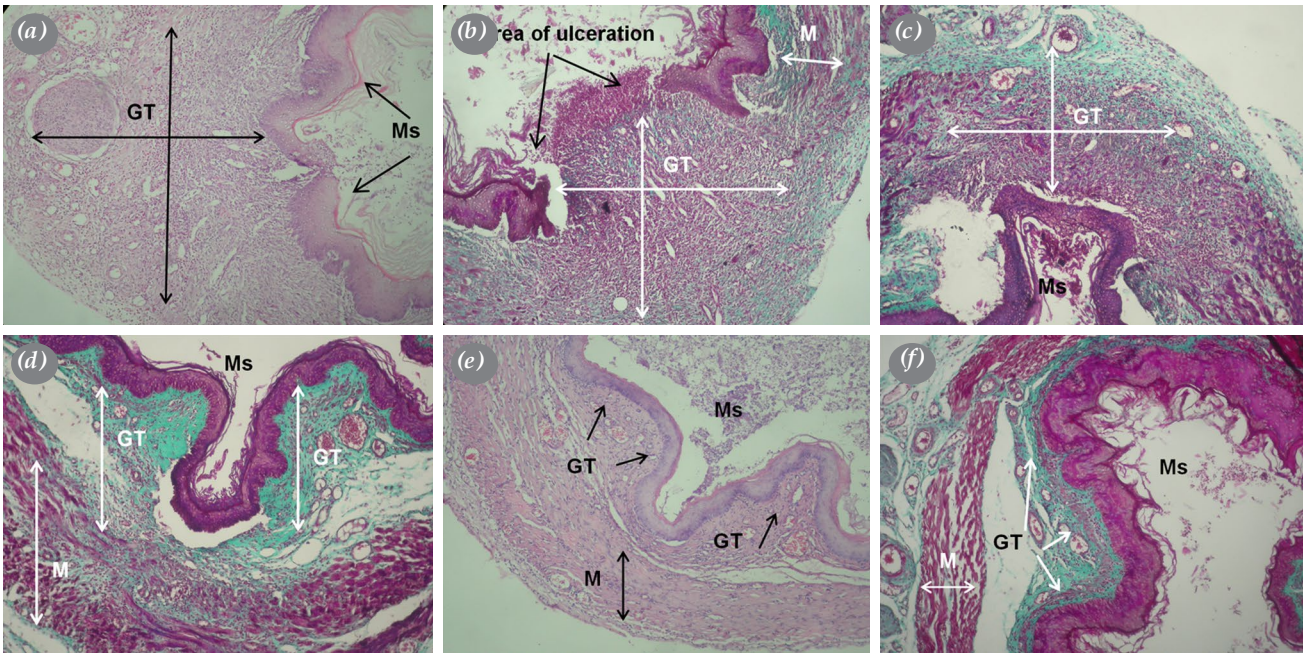

Figure 2. (a) Control group, the development of an intensive GT with complete re-epithelialization, but covering all the layers (Grade 2) are seen (H&E, ×40). **(b)** Control group, a development of intensive GT with incomplete re-epithelialization is present (MTC, ×100). **(c)** MP group, a development of less intensive GT with incomplete epithelialization is seen, compared to controls (MTC, ×100). **(d)** SCF group, a development of intensive GT with complete re-epithelialization and also including partly superficial, limited to submucosa is seen (MTC, ×100). **(e)** ALA group, that epithelium margins due to the decrease of inflammation prevalence are well-preserved, and granulation tissue is restricted (H&E, ×40). **(f)** ALA group, granulation tissue is less prevalent and severe, as the occurrence of tissue injury is limited to submucosa, and complete re-epithelization is also improved (MTC, ×100).

GT: Granulation tissue; MP: Methylprednisolone; ALA: Alpha lipoic acid.

Table 4. Simultaneous comparison of GSH levels of the groups

	Mean difference	Standard error	*p*
Group 1			
Group 2	-1.095032	0.190978	0.001
Group 3	-0.354768	0.196131	0.290
Group 4	-0.577893	0.196131	0.031
Group 2			
Group 1	1.095032	0.190978	0.001
Group 3	0.740264	184142	0.002
Group 4	0.517139	0.184142	0.042
Group 3			
Group 1	0.354768	0.196131	0.290
Group 2	-0.740264	0.184142	0.002
Group 4	-0.223125	0.189480	0.646
Group 4			
Group 1	0.577893	0.196131	0.031
Group 2	-0.517139	0.184142	0.042
Group 3	0.223125	0.189480	0.646

The extensity of inflammation was determined not to cover all layers in the SCF and MP groups (n=5, 62.5%, and n=4, 50.0%) (Figure 2e, f).

When the scores of fibrosis were examined, fibrosis severity was found to be the highest in controls with 85.7% (n=6) (Figure 2a), compared to the other groups. The fibrosis severity and fibrosis extent scoring scores as assessed histopathologically are shown in Table 3. While the rate of fibrosis severity was 77.8% (n=7) in the ALA group, it was 50.0% (n=4) and 37.5% (n=3) in the SCF and MP groups, respectively. Fibrosis extent scoring was also evaluated. As Grade 0 was not detected in the groups, the difference was not statistically significant ($p>0.05$). According to their percentiles, the extensity of fibrosis existed with the rate of 85.7% (n=6) in all layers of the controls, with the rate of 50.0% (n=4) in the MP group, with the rate of 37.5% (n=3) in the SCF group, and with the rate of 22.2% (n=2), the lowest rate, in the ALA group. Submucosal or focal fibrosis extensity was determined to be excellent in the ALA group with the rate of 77.8% (n=7) and very poor in controls with the rate of 14.3% (n=1), whereas it was 62.5% (n=5) in the SCF group and 50% (n=4) in the MP group.

For GSH evaluation, although a significant difference was found between the ALA group (1.20±0.54) and other groups, there was no significant difference between the MP (0.46±0.17) and SCF groups (0.68±0.44). The GSH levels of the groups were compared simultaneously (Table 4). Therefore, ALA increased the level of GSH, indicating a statistically significant difference ($p<0.05$). The levels of tissue hydroxyproline (HP) were found to be the lowest in the ALA group with the rate of 7.08±0.66 and the highest in controls with the rate of 7.08±0.66. Based on these findings, ALA decreased significantly the level of tissue HP, but not MP and SCF.

DISCUSSION

Corrosive esophagus burns are still a severe health problem due to its frequent occurrences and causing high rates of mortality and morbidity. The most frequent and unprevented complications of CEBs are esophagus strictures. In CEBs, changes from minimal mucosal injuries to whole-layer necrosis on esophagus wall occur. Since the development of stenosis following CEBs causes the stricture in esophagus, studies are mostly focused on decreasing and preventing the development of stenosis. Although many agents, including retinoic acid, pentoxifylline, SCF, N-acetylcysteine, antibiotics, and steroids have been used in both clinical and experimental studies to prevent the development of strictures, only antibiotics and steroids have gained clinical application.[11] The main goals of treatment in CEBs are to reduce the burn event that causes damage, to reduce bacterial colonization that may occur in the damaged epithelium, and to prevent stenosis. Currently, to reduce or prevent stenosis, steroids and broad-spectrum antibiotics are started in the early period, dilatation treatments and surgical treatments are used to reduce stenosis. Effective treatment options have not been realized. Although mucosal necrosis is involved in the development of strictures in corrosive esophagus, the inflammatory response of the tissue is also of a vital part in the development of strictures. During the first 48 h of burns, hemorrhage, thrombosis, edema and local necrosis occur in tissues. In the regions where the corrosive substance has an impact, necrosis of liquefaction occurs, and the condition goes on until the absorbed alkali is neutralized. The occurred free oxygen radicals (FORs) enhances tissue damage affecting cells and their membranes trough lipid peroxidation. The FOR increases in burned tissue within the first 72 h after the exposure in corrosive esophagus. In the light of literature, the development of the strictures could be prevented by decreasing inflammation process with the inactivation of FOR at the early stage of wound healing, and positive findings are present, related to the decrease in the index of inflammation and stenosis.[12-14] The epithelial changes (necrosis and regeneration), inflammation, fibrosis (intensity and extent) and stenosis index were evaluated histopathologically in the corrosive esophageal model.[15]

In our study, ALA, an antioxidant substance[16] to be an alternative in the treatment of corrosive esophagus, was compared with MP and SCF that are still in use. It has been reported that vitamins C and E[12] and trimetazidine reduce stricture.[17] Ulceration rates were lower in the ALA group compared to the other groups, and complete re-epithelialization was excellent in this group. The severity of inflammation was the second excellent in the ALA group after the SCF group. With regard to the extensity of inflammation, the results were found to be excellent obtained in the group treated with ALA. In relation to the severity and extensity of fibrosis, the ALA group had the excellent results. As a result of the findings, it is considered that ALA decreases inflammation through antioxidant mechanisms and can decrease strictures. The SCF had a preventive effect on the development of strictures and could be a therapeutic choice to increase mucosal improvement.[18] In a study investigating the effect of SCF on stricture formation

in rats with experimental CEBs, 50 mg/100 g orally twice a day was administered.[19] It was reported that SCF had an inhibitory effect on the formation of structure and increased mucosal healing in rats given SCF. From the data obtained in our study, it was remarkable that SCF, particularly due to its superficial protective effect on mucosa, leads to a marked microscopic amelioration in corrosive esophagus segment after the ALA group.

Steroids and antibiotics are the most frequently used drugs for CEBs. However, the definite effects of these drugs on preventing the development of stenosis have not been demonstrated. In addition, there are differences of opinion on the drug to be chosen in the treatment, the dose and the duration of the treatment. Like all corticosteroids, the MP keeps the protein synthesis of cells in certain tissues under control and has anti-inflammatory and anti-allergic effects. It also inhibits the growth of neutrophil and monocyte macrophages at the site of inflammation. It reduces the number and proliferation of fibroblasts in the connective tissue, suppressing the immune system. In a prospective study with broad series, the use of prednisolone (2 to 4 mg/kg) for three to six weeks was reported not to decrease the formation of stricture.[20] In the wound healing, the infection developing in burned tissue is known to increase basically the formation of stricture as a result of inflammatory reaction. Therefore, the administration of antibiotics at an early stage for cases admitted with the absorption of corrosive substances is a globally accepted and suggested application.[21,22] Özel et al.[23] used L-arginine and N-nitro-L-Arginine methyl ester (L-NAME), which they thought to reduce FOR, nitric oxide, and endothelin injury in experimental CBC-induced rats. As a result, they revealed that L-arginine and L-NAME had a reducing effect on the severity of injury in the early stages. It was suggested that, in the prevention of the development of stenosis after CEBs, the treatment with corticosteroids became an abandoned option, the formation of stricture started to develop in minutes after exposure to corrosive substances in many cases, and the following therapeutic procedure was of a limited effect.[24] In our study, the severity and extent of inflammation and ulceration were higher in the subacute period in the MP group.

The GSH protects cells against oxidative damage due to the reaction to free radicals and peroxides. Kumbasar et al.[25] reported that they detected the GSH level in their study using ALA. In our study, blood GSH values were found to be significantly higher in the ALA group compared to the other groups. It is thought that high GSH level in the subacute period would reduce the severity of the injuries in the early period, thereby preventing the formation of stenosis in the future. We consider that the increase in the amount of collagen is responsible for the formation of scar tissue in CEBs. In parallel with the increase in collagen in the tissues, the tissue HP level increases. Therefore, tissue HP levels are an objective parameter that indirectly reflect the level of collagen in tissues.[26,27] In our study, the lowest level was seen in the ALA group. Ozçelik et al.[28] in their study investigating the effects of halofuginone, a specific inhibitor of type 1 collagen synthesis, the major component of fibrosis, on esophageal structure formation in experimental CEBs, reported that HP levels decreased significantly in the treated group and a specific inhibitor of type 1 collagen synthesis, halofuginone, reduced the formation of esophageal structure.

The limitation of ALA treatment in corrosive esophageal burns was that the oral form of ALA could not be used and the intraperitoneal form was prepared and used because of the difficulty of intravenous administration. In order to investigate the long-term effects of ALA treatment, it may be more effective to use the intravenous form in experimental studies. Another limitation was the laparotomy in the corrosive esophageal creation technique. During this surgical procedure, the possibility of adverse effects due to hypothermia due to prolongation of the surgery was increased, and it also required particularly good care in the postoperative period. Therefore, there is a need for new experimental models for esophageal burns without additional surgical procedures. This study is a study that offers both experimental and clinical treatment alternatives with the development of new models.

In conclusion, alpha lipoic acid decreases ulceration, inflammation, the extensity of inflammation and the severity and extensity of fibrosis in corrosive esophageal burns in the subacute period, increases the level of blood glutathione, is beneficial in the clearance of free oxygen radicals at early stages and, as a result of such mechanisms, decreases the formation of damage to tissues, and long-term consequences would also reduce the formation of strictures. However, further clinical studies are needed to confirm these findings.

Ethics Committee Approval: This study was carried out in the Experimental Medicine and Application Center of the Selçuk University Meram Medical Faculty. Pathology specimens were examined in the Department of Histology and Embryology, Meram Medical Faculty, Necmettin Erbakan University. The study protocol was approved by Selçuk University Meram Medical Faculty, Experimental Medicine and Application Center, Laboratory Animals Ethical Boar

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, literature review, writing the article, references and fundings: G.M.; Control/supervision: C.S.; Data collection and/or processing: G.M., G.B.; Analysis and/or interpretation, materials: G.M., C.S., G.B.; Critical review: G.B.

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