

Investigation of the protective effect of adalimumab on stricture and inflammation in an experimental corrosive esophageal burn model in rats

Investigación del efecto protector del adalimumab sobre la estenosis y la inflamación en un modelo experimental de quemadura esofágica por cáusticos en ratas

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Abstract

Objectives: This study aimed to investigate the effectiveness of the tumor necrosis factor- α inhibitor adalimumab on inflammation and subsequent stricture development in a corrosive esophageal burn model in rats, based on its antifibrotic effect in Crohn's disease. **Methods:** Forty-eight female Wistar Albino rats were randomized into four groups ($n = 12$): control, local intraluminal adalimumab (5 mg/kg), systemic subcutaneous adalimumab (5 mg/kg), and combined local plus systemic adalimumab. A corrosive esophageal burn was created in all animals. After 10 days, the distal esophageal segment was excised and evaluated by stenosis index (SI), histopathologic damage score (HDS), and tissue hydroxyproline level. Data were analyzed using non-parametric tests. **Results:** Compared with the control group, the systemic and combined groups showed a significant reduction in SI and hydroxyproline level ($p < 0.05$). The combined group also reduced HDS. Local adalimumab showed no difference from the control. **Conclusions:** Systemic adalimumab reduced inflammation and stenosis in corrosive esophageal burns, whereas local administration had no significant effect. Further clinical studies are needed before adalimumab can be considered for these injuries.

Keywords: Adalimumab. Esophageal stenosis. Caustics. Tumor necrosis factor- α . Rats.

Resumen

Objetivo: Investigar la eficacia del adalimumab, un inhibidor del factor de necrosis tumoral alfa, sobre la inflamación y el desarrollo de estenosis en un modelo de quemadura esofágica por cáusticos en ratas, a partir de su efecto antifibrótico en la enfermedad de Crohn. **Métodos:** Se aleatorizaron 48 ratas hembra Wistar Albino en cuatro grupos ($n = 12$): control, adalimumab local intraluminal (5 mg/kg), adalimumab sistémico subcutáneo (5 mg/kg) y adalimumab combinado local más sistémico. Se creó una quemadura esofágica por cáusticos en todos los animales. A los 10 días se extirpó el segmento esofágico distal y se evaluó mediante el índice de estenosis, la puntuación de daño histopatológico y el nivel tisular de hidroxiprolina. Los datos se analizaron mediante pruebas no paramétricas. **Resultados:** Frente al grupo control, los grupos sistémico y combinado mostraron una reducción significativa del índice de estenosis y del nivel de hidroxiprolina ($p < 0.05$). El grupo combinado también redujo la puntuación de daño histopatológico. El adalimumab local no mostró diferencias respecto al control. **Conclusiones:** El adalimumab sistémico redujo la inflamación y la estenosis en las quemaduras esofágicas por cáusticos, mientras que la administración local no tuvo efecto significativo. Se necesitan más estudios clínicos antes de considerar el adalimumab para estas lesiones.

Palabras clave: Adalimumab. Estenosis esofágica. Cáusticos. Factor de necrosis tumoral alfa. Ratas.

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Introduction

Corrosive esophageal burns are a significant health problem, particularly in developing countries. They commonly occur accidentally in children and as a result of suicide attempts in adults; because larger volumes are usually ingested in suicide attempts, more severe esophageal and gastric injuries result.¹ Recent data indicate that more than 200,000 exposures to household or industrial cleaning products occur annually in the United States, and that corrosive esophageal burns affect approximately 5000-15,000 people each year.²

Approximately 20-40% of caustic ingestions result in esophageal damage.³ The injury may lead to early perforation and, more frequently, to late stricture formation. The aim of treatment is to support wound healing, prevent perforation, and reduce stricture formation. Once a stricture forms, patients often require repeated endoscopic dilations, stenting, or major surgical procedures such as total esophagectomy and colonic interposition, all of which carry high morbidity and mortality. Corrosive injury to the upper gastrointestinal tract therefore remains a major surgical dilemma.⁴ Although many agents have been investigated, no effective and satisfactory medical treatment to prevent or at least reduce stricture formation has been established.

Adalimumab is a monoclonal antibody that specifically blocks the interaction of tumor necrosis factor- α (TNF- α) with its cell-surface receptor. As a selective TNF- α inhibitor, adalimumab not only reduces intestinal fibrosis in Crohn's disease but is also effectively used in the treatment of chronic diseases such as rheumatoid arthritis, psoriasis, and uveitis.⁵ TNF- α is a pro-inflammatory cytokine and a key mediator of inflammatory bowel disease, with elevated levels demonstrated in the intestinal wall.

In this study, we aimed to investigate the effectiveness of the TNF- α inhibitor adalimumab on inflammation and subsequent stricture development in corrosive esophageal burns in rats by inhibiting TNF- α release. We hypothesized that this drug, which reduces inflammatory narrowing of the intestinal lumen in patients with Crohn's disease, might also have a protective effect on esophageal stricture formation.

Methods

This study was conducted at the Experimental Animal Breeding and Research Unit of Uludağ University,

and tissue specimens were examined at the Department of Pathology, Faculty of Veterinary Medicine, Uludağ University. After the study protocol was established, approval was obtained from the Uludağ University Local Animal Experiments Ethics Committee (Decision No: 2022-11/03). The study was conducted in accordance with institutional and national guidelines for the care and use of laboratory animals, and reporting follows the ARRIVE 2.0 guidelines.

Forty-eight female Wistar Albino rats weighing 250-300 g were used. The animals were housed in standard cages (3-4 per cage) for 7 days at 21-24°C with 50% humidity and a 12-h light/dark cycle, and were provided with a standard pellet diet and tap water *ad libitum*. After acclimatization, the animals were randomized into four groups of 12 using a simple randomization method based on a random number table. A relatively small group size was chosen deliberately because mortality was expected during the 10-day follow-up period; the sample size was based on comparable previously published experimental corrosive esophageal burn studies, and no formal a priori power calculation was performed. Solid food and water were withdrawn 2 h before anesthesia. The experimental groups are shown in table 1.

Anesthesia and corrosive esophageal burn technique

After 2 h of fasting, the animals were weighed. General anesthesia was induced with sevoflurane (2-8% in gaseous form). The rats were then placed in the supine position and secured by their four limbs, and the surgical area was disinfected with an antiseptic solution. The adequacy of anesthesia was tested before the procedure was started.

To create the corrosive esophageal burn model, the method first described by Gehanno and Guedon⁶ and later modified by Bakan et al.⁷ was used, aiming to produce a burn by delivering the corrosive agent to each subject under equal pressure. Following laparotomy, the stomach and distal esophagus were exposed. A two-way 5 Fr catheter was advanced orally into the distal esophagus. To ensure that the agent produced a burn only in the distal esophagus, the distal and proximal ends of the gastroesophageal junction were ligated with 2-0 silk to prevent leakage into the distal stomach and proximal esophagus. Both lumens of the catheter remained within the isolated esophageal segment. To create the burn, 40% sodium

Table 1. Experimental groups

Group	n	Treatment
Control	12	No treatment
Local TNF- α	12	Local (intraluminal) adalimumab 5 mg/kg
Systemic TNF- α	12	Systemic (subcutaneous) adalimumab 5 mg/kg
Local + systemic TNF- α	12	Both local and systemic adalimumab 5 mg/kg

TNF- α : tumor necrosis factor- α .

hydroxide (NaOH) was instilled through one lumen of the catheter into the closed esophageal segment, and a manual manometer connected to the other lumen was used to maintain an intraluminal pressure of 20 cmH₂O in each animal (Fig. 1). The same intraluminal pressure was maintained in all subjects throughout the procedure. After 60 s, the agent was aspirated, and the segment was irrigated with distilled water for 30 s. The ligatures were then released, the catheter was withdrawn orally, and the abdomen was closed in a standard fashion. All animals received post-operative analgesia to minimize pain and distress. The animals were not fed for 24 h after the procedure and then returned to their normal daily routines.

Sacrifice and tissue sampling

No exclusion criteria were established a priori; animals were excluded on a case-by-case basis if they died before the scheduled sacrifice. Three rats from the control group and two rats from each of the other groups died before sacrifice for various reasons (wound dehiscence, inability to feed, esophageal perforation, aspiration, etc.) and were excluded. After 10 days, the remaining rats were weighed under anesthesia and then sacrificed. The abdominal cavity was opened together with the sternum, and the distal 2 cm segment of the esophagus where the burn had been created was excised. The specimen was divided into two parts: One was reserved for tissue hydroxyproline measurement, and the other was placed in 10% neutral formaldehyde for pathological and histological examination.

To fix the esophageal lumen, 10% neutral formaldehyde was used, followed by paraffin embedding; 4 μ m sections were stained with hematoxylin-eosin and examined under a light microscope. The stenosis index (SI) was used to assess esophageal stenosis.

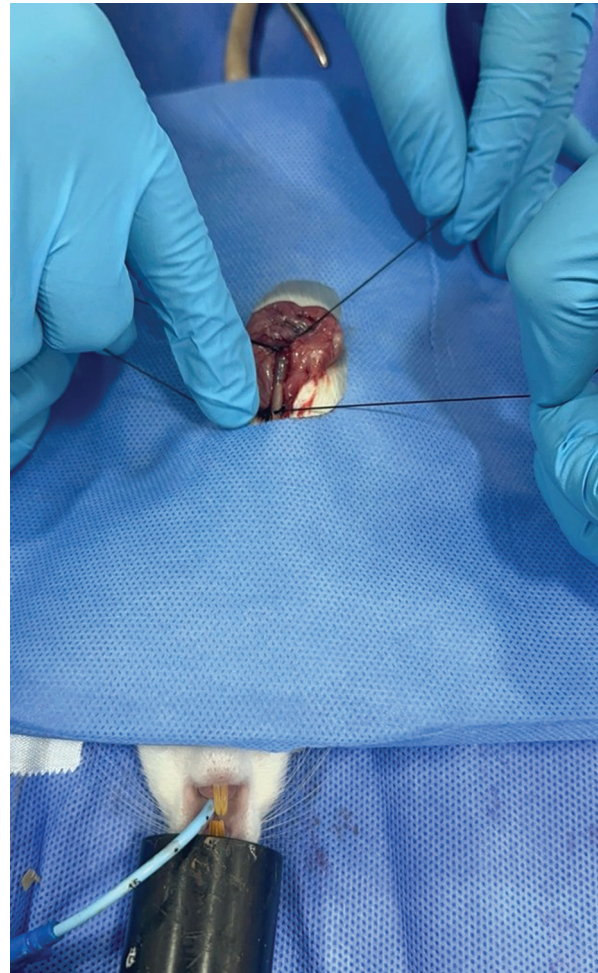


Figure 1. Experimental setup of the corrosive esophageal burn model. The two-way catheter is connected to a manual manometer to maintain a constant intraluminal pressure of 20 cmH₂O during instillation of the corrosive agent.

Esophageal wall thickness was measured at two different areas using a millimetric ocular micrometer, from the muscularis mucosa to the connective tissue beyond the muscularis propria, and the mean was calculated ($A0 = [A1 + A2]/2$). Luminal diameters were measured at two different areas and averaged ($B0 = [B1 + B2]/2$). The SI was obtained by dividing wall thickness (A0) by luminal diameter (B0) (Fig. 2).

The histopathologic damage score (HDS) was used to assess tissue injury in the esophageal wall. Paraffin-embedded blocks were stained with Masson's trichrome, and scoring was performed in three categories (increase in submucosal collagen, damage to the muscularis mucosa, and damage to the tunica muscularis) (Figs. 3 and 4). All histopathological evaluations were performed by a pathologist who

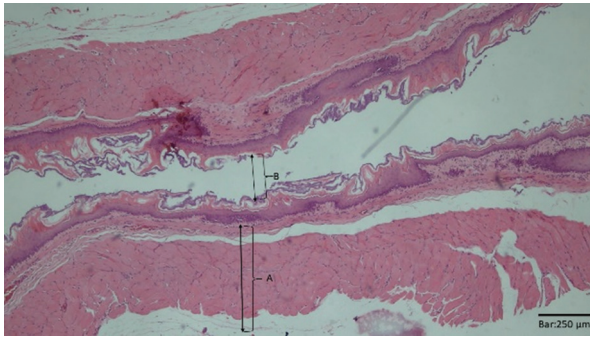


Figure 2. Calculation of the stenosis index. **A:** esophageal wall thickness. **B:** luminal diameter. Hematoxylin-eosin. Scale bar: 250 μ m.

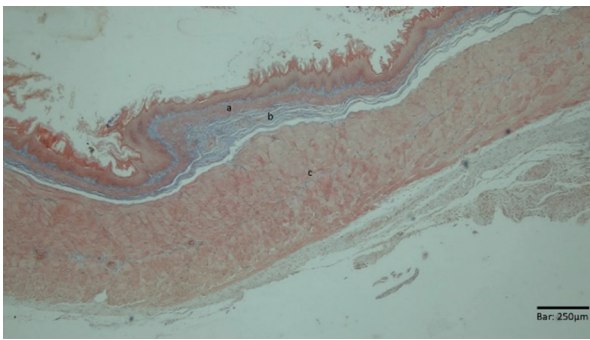


Figure 3. Esophageal cross-section showing the layers assessed in the histopathologic damage score. **A:** Muscularis mucosa. **B:** Submucosal collagen. **C:** tunica muscularis. Masson's trichrome. Scale bar: 250 μ m.

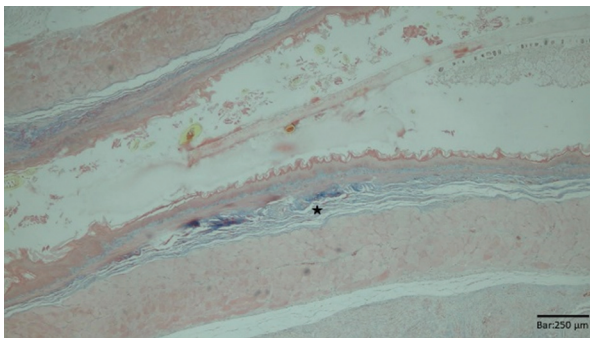


Figure 4. Increase in submucosal collagen (star), corresponding to a damage score of 2. Masson's trichrome. Scale bar: 250 μ m.

was blinded to the group allocation of the specimens. Tissue hydroxyproline levels were measured in a specialized biochemistry laboratory using a spectrophotometric method; as hydroxyproline is a component of collagen fibers, it serves as an indicator of collagen turnover.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 20.0 (IBM Corp., Armonk, NY). The normality of variable distributions was assessed using visual methods (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). As the variables did not show a normal distribution, descriptive analyses were presented as median and range, and comparisons among groups were performed using the Kruskal-Wallis test. Pairwise comparisons were performed using the Mann-Whitney U test with Bonferroni correction. A $p < 0.05$ was considered statistically significant.

Results

Body weight

The body weights of the animals were measured before the procedure and immediately before sacrifice. When pre- and post-procedure weights were analyzed using the Kruskal-Wallis test, the weight distributions were similar across all groups. Although there was no statistically significant change in median weight within the groups, a decrease in median weight was observed in the control group, whereas a slight increase in mean post-procedure weight was observed in the groups receiving local and combined local plus systemic treatment.

SI

The difference between the control group and the systemic treatment group, and between the control group and the combined local plus systemic treatment group, was statistically significant ($p = 0.016$ and $p = 0.007$, respectively). No significant differences were found in the other pairwise comparisons. The median SI decreased progressively from the control group (2.16) to the systemic (1.15) and combined (1.06) groups.

HDS

The difference between the control group and the combined local plus systemic treatment group was statistically significant ($p = 0.041$). No statistically

significant differences were observed in the other pairwise comparisons.

Tissue hydroxyproline

In the comparison of tissue hydroxyproline levels, statistically significant differences were noted between the control group and the systemic treatment group, and between the control group and the combined treatment group ($p = 0.001$ and $p = 0.020$, respectively). No significant differences were observed in the other pairwise comparisons.

All results are presented together in tables 2 and 3.

Discussion

Corrosive esophageal burns are a serious health problem associated with considerable morbidity and mortality. The most frequent and incompletely preventable complication is esophageal stricture. Although the number of hospital admissions has decreased over the past 30 years in developed countries, these injuries are still frequently encountered in our country.¹ In corrosive esophageal burns, severe changes ranging from minimal mucosal injury to transmural necrosis of the esophageal wall can occur. Clinical studies have shown that 75-95% of ingested corrosive liquids are alkaline, and the distal esophagus is the region where the burn is most intense; for this reason, we created the burn model in the distal esophagus.³ This is also why NaOH was chosen to create the burn model, as alkalis such as potassium hydroxide, sodium hydroxide, and sodium hypochlorite account for 75-90% of clinically encountered corrosive esophagitis.²

Because the main problem in corrosive esophageal burns is esophageal stricture, studies have generally focused on treatments that prevent or reduce stricture development. Despite various treatments, 7-15% of caustic burns still result in esophageal stricture. Many experimental treatments have been reported, but no effective treatment has yet been established. Various agents have been investigated for the prevention of esophageal stricture, including penicillamine,⁶ colchicine,⁸ N-acetylcysteine,⁹ indomethacin,¹⁰ heparin,¹¹ estrogen and progesterone,¹² antioxidants such as Vitamins E and C,¹³ and epidermal growth factor (EGF) and interferon gamma.¹⁴ However, no significant clinical success has been achieved, partly because results from different burn models are not

always clinically applicable and because many of these agents have multiple side-effect mechanisms.

TNF- α is one of the critical factors mediating inflammatory and immunological responses to stress, infection, and injury. Its wide range of effects includes growth-promoting activity on fibroblasts, leading to increased local collagen deposition.¹⁵ TNF- α has been reported to be associated with other mediators regulating inflammation and fibrosis in CCl₄-induced hepatotoxicity,¹⁶ and antibodies against TNF- α have been shown to prevent concanavalin A-induced hepatic fibrosis in rodent models.¹⁷ Increased levels of TNF- α have also been demonstrated in radiation-induced esophageal strictures.¹⁸ We therefore hypothesized that inhibition of TNF- α would reduce fibrosis development during the healing phase of alkaline esophageal burns.

Anti-TNF therapies have complex immunomodulatory effects and may be beneficial in various inflammatory conditions.¹⁹ Adalimumab has been shown to be effective in the inflammatory stenosis of Crohn's disease.⁵ In an experimental study on corrosive esophageal burns, Yukselen et al. reported that infliximab was not effective.²⁰ In contrast, the results of our study demonstrated that systemic use of adalimumab for TNF- α inhibition reduced inflammation and stenosis in corrosive esophageal burns in rats. The difference between our findings and those reported for infliximab may be related to differences between the two anti-TNF agents, since adalimumab is a fully human monoclonal antibody whereas infliximab is chimeric, as well as to differences in dosing and administration protocols. A further consideration is that adalimumab is an agent already approved for human use with a well-characterized safety profile, which may favor its eventual clinical translation compared with purely experimental agents.

The lack of effect of locally administered adalimumab, in contrast to the systemic route, is noteworthy. In the literature, the few studies on the local use of adalimumab are mostly in the form of injections for perianal Crohn's disease, and its efficacy remains controversial.²¹⁻²⁴ In our study, we could not demonstrate any significant effect of local adalimumab administration on inflammation or stricture formation. This may be related to insufficient absorption or penetration of the locally applied agent through the damaged mucosa, local proteolytic degradation, or the possibility that the principal effect of TNF- α inhibition is mediated through the systemic inflammatory cascade rather than locally.

Table 2. Summary of outcome measures by group, expressed as median (minimum–maximum)

Variable (median [min-max])	Control (n = 9)	Local (n = 10)	Systemic (n = 10)	Local + systemic (n = 10)
Stenosis index	2.16 (1.50-4.16)	1.86 (0.53-3.83)	1.15 (0.45-2.18)	1.06 (0.31-2.81)
Histopathologic damage score	4 (2-5)	3 (2-5)	3 (1-5)	2.5 (1-4)
Hydroxyproline (µg/mg)	1.21 (0.87-1.41)	0.90 (0.73-1.12)	0.76 (0.61-0.92)	0.79 (0.60-0.95)
Pre-procedure weight (g)	274 (236-287)	236 (212-305)	246 (216-290)	239 (214-279)
Post-procedure weight (g)	230 (210-265)	242 (176-284)	235 (180-262)	250 (220-275)

Table 3. Pairwise comparisons between groups (Mann-Whitney U test)

Comparison (p)	C versus L	C versus S	C versus L + S	L versus S	L versus L + S	S versus L + S
Stenosis index	0.954	0.016*	0.007*	0.609	0.358	1.000
Histopathologic damage score	1.000	0.211	0.041*	1.000	0.485	1.000
Hydroxyproline	0.317	0.001*	0.020*	0.168	0.538	1.000

*p < 0.05. C: control; L: local; S: systemic; L + S: local plus systemic.

Limitations

This study has several limitations. First, the relatively small number of animals per group, further reduced by procedure-related mortality, may have limited the statistical power to detect differences between some treatment arms; thus, the absence of a significant effect in the local treatment group should be interpreted as a failure to detect an effect rather than definitive proof of no effect. Second, only female rats were used, and sex-related differences in the fibrotic or inflammatory response cannot be excluded. Third, a single dose level of adalimumab (5 mg/kg) was tested, so the dose-response relationship and the optimal therapeutic dose remain undetermined. Fourth, the follow-up period was limited to 10 days, which captures the acute inflammatory phase but may not fully reflect the late fibrotic and stricture-forming process. Finally, as an experimental animal study, these findings cannot be directly extrapolated to clinical practice.

Further evaluation of the inflammatory and immunological events leading to stricture formation in corrosive esophageal burns, as well as advanced studies targeting the blockade of other inflammatory cytokines such as transforming growth factor- β 1, platelet-derived growth factor, EGF, fibroblast growth factor, and interleukin-1, may provide new perspectives for treatment.

Conclusions

There is still no definitive treatment that effectively reduces the burn and its complications in corrosive esophageal burns. In our study, systemic administration of adalimumab reduced inflammation and stenosis, whereas local intraluminal use had no significant effect on inflammation or stenosis. Further clinical studies are needed to evaluate the experimental use of adalimumab in corrosive esophageal burn cases.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that they have followed the ethical standards of the relevant experimentation committee, according to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

This experimental study was approved by the Uludağ University Local Animal Experiments Ethics Committee (Decision No: 2022-11/03) and was conducted in accordance with institutional and national guidelines for the care and use of laboratory animals. The study did not involve human participants. Reporting adheres to the ARRIVE 2.0 guidelines for animal research.

Declaration on the use of artificial intelligence. The authors declare that Claude was used for figure legends.

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