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The comparison of prednisolone and honey activities in the experimental corrosive esophagitis model

Deneysel koroziv özofajit modelinde prednisolon ve balın etkinliklerinin karşılaştırılması

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Abstract

Aim: Honey is well known for its beneficial wound healing-related effects, including anti-edematous effects, stimulation of granulation tissue formation, chemical debridement, and immune system enhancement. In this experimental study, the effects of honey and prednisolone on stricture formation in sodium hydroxide-induced corrosive esophagitis were investigated.

Methods: This study was carried out on Wistar albino rats weighing between 200-250 grams. Rats were divided into four equal groups. Corrosive esophagitis induced by 37.5% sodium hydroxide was formed in three groups. The first group received no specific treatment. The second group was treated with honey via the oral route, and the third group was treated by prednisolone intraperitoneally. The control group underwent a sham laparotomy. All subjects were sacrificed by the end of the 28th day. A 20-mm long segment of the distal esophagus was harvested for histopathological examination. The tissue damage scores and stenosis index scores of the groups were measured and compared.

Results: A total of 32 rats were included in the study, with eight subjects in each group. The mean values of stenosis index score and tissue damage score were significantly lower in the honey-treated group (P=0.001).

Conclusion: Oral honey treatment seems to reduce the severity of esophageal strictures associated with corrosive esophagitis, when compared to untreated and prednisolone-treated groups.

Keywords: Caustic esophageal burn, Corrosive esophagitis, Honey, Prednisolone, Stricture, Stenosis index, Tissue damage

Öz

Amaç: Bal antiödem etkisi, granülasyonu hızlandırıcı etkisi, enzimatik debridman ve immün sistemi güçlendirici etkisi bilinen bir doğal gıdadır. Bu deneysel çalışmanın amacı bir alkali ajan olan sodyum hidroksit ile oluşturulan koroziv özofajitte darlık gelişimi üzerine balın ve prednisolonun etkilerini araştırıldı.

Yöntemler: Bu çalışma, ağırlıkları 200-250 gram arasında değişen Wistar tipi albino sıçanlar üzerinde gerçekleştirildi. Denekler, eşit sayıda dört gruba bölündü. Birinci, ikinci ve üçüncü gruplar özofajit modeli grupları olup, bu gruplardaki tüm deneklerde %37,5'luk sodyum hidroksit ile koroziv özofajit oluşturuldu. Birinci gruba herhangi bir tedavi uygulanmazken, ikici gruba oral bal tedavisi ve üçüncü gruba intraperitoneal prednisolon tedavisi uygulandı. Kontrol grubunun özofagusuna herhangi bir işlem yapılmadan şam laparotomi uygulandı. Tüm denekler 28. gün sakrifiye edildi ve deneklerin distal özofaguslarından alınan 20 mm uzunluğundaki örnekler histopatolojik incelemeye tabi tutuldu. Grupların doku hasarı skorları ve stenoz indeksi skorları ölçülerek kıyaslandı.

Bulgular: Çalışmaya toplam 32 denek dahil edildi ve her bir grupta sekiz denek mevcuttu. Stenoz indeksi skoru ortalama değeri ve doku hasarı skoru ortalama değeri balla tedavi edilen grupta, prednisolon verilen ve tedavi verilmeyen gruplara kıyasla anlamlı olarak düşüktü (P=0,001).

Sonuç: Bal, prednisolona kıyasla, alkalen ajanla oluşturulan deneysel koroziv özofajit modelinde gelişen özofagus darlıkları üzerinde daha anlamlı düzeyde olumlu etkiye sahiptir.

Anahtar kelimeler: Kostik özofagus yanığı, Koroziv özofajit, Bal, Prednisolon, Darlık, Darlık indeksi, Doku hasarı

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Introduction

Burn injuries in the esophagus caused by drinking strong acid and alkaline substances are generally seen more in pre-school age children and the elderly in developing countries [1]. The scar tissue that develops during the healing process causes a narrowing of the esophagus as with any burn, which leads to severe problems in the patient's quality of life, morbidity, and even mortality [2].

Treatment of strictures related to esophageal burns have been studied since the beginning of last century. A few methods have been proven successful in the studies on clinical treatments, except for dilatation and local steroid injection. Those that are accepted as relatively successful are still a long way from being the ideal treatment method. Therefore, experimental research has started using various substances and materials on animal burn models. Apart from steroids, materials that have been found to be largely successful have not been introduced into practical use in the clinic. The reasons for this are partially due to toxicity, cost, and availability problems, and the main reason is that they have not been proven safe for human use [3].

Since treatment is difficult after the formation of burn strictures, the research on treatment must be aimed at preventing stricture formation following the burn. Stricture development occurs with the development of excessive collagen during the healing process and negative wound healing [4].

Since the ancient times, honey has been used in the treatment of various diseases, especially wound care. It has been advocated as a foodstuff with high nutrient content, having properties that accelerate wound healing, such as high viscosity, acidic pH, high osmolarity and hydrogen peroxide, all of which engage in bacterial growth inhibition [5]. Numerous studies have shown that honey also suppresses free radical production [6]. There are many studies demonstrating that granulation is prevented, and stricture formation is decreased by steroidal components [7-9].

The aim of this experimental study was to investigate the effects of honey and prednisolone on stricture formation in sodium hydroxide-induced corrosive esophagitis in a rat model.

Materials and methods

Study design

This experimental study was conducted in the Experimental Medicine and Research Center of the University after approval was obtained from the Local Animal Research Ethics Committee. All procedures in the study were performed in accordance with the principles of the Guidelines for Animal Research of the Ethics Committee.

A total of 32 female Wistar albino rats, each weighing 200–250 g, were randomly separated into four groups of eight rats. All animals were kept in metal cages at a room temperature of 22˚C and a 12-h light-dark cycle. The rats that were to undergo laparotomy were fasted starting on the morning of the procedure.

Forming the model of chemical esophagus burn

Laparotomy was performed after the administration of intraperitoneal anesthesia with 40 mg/kg sodium thiopental. Abdomen was entered with a 2-cm midline incision, and a 20 mm-long segment of the abdominal esophagus was prepared. A 6F catheter, 48 mm in length, was passed through the mouth and placed in the upper segment of the abdominal esophagus. To prevent aspiration of the corrosive agent into the respiratory system, the esophagus was sutured with 2/0 silk immediately proximal to and below the diaphragm. A solution of 1 ml 37.5% NaOH (pH=12) prepared for the 90 sec period after catheter placement was then administered to the esophagus. The burnt segment was irrigated for 60 seconds with distilled water. The proximal 2/0 suture was cut, and catheter was withdrawn from the mouth with negative pressure to prevent aspiration. The distal 2/0 suture was then cut, and laparotomy incision was closed (Gehanno and Gudeon Model) [10,11].

Study groups

Group 1 (Burn, n=8): Corrosive esophagitis was induced. Animals were kept under standard laboratory conditions and fed for 28 days with free access to standard pellet food and tap water.

Group 2 (Burn +Honey, n=8): Corrosive esophagitis was induced, and the animals were administered honey via gavage once a day starting on postoperative Day 1. The rats were kept under standard laboratory conditions and fed for 28 days with free access to standard pellet food and tap water.

Group 3 (Burn+Prednisolone, n=8): Corrosive esophagitis was induced, and the animals were administered 1 mg/kg/day intraperitoneal prednisolone daily, starting from postoperative Day 1. The rats were kept under standard laboratory conditions and fed for 28 days with free access to standard pellet food and tap water.

Group 4 (Sham laparotomy group–control group, n=8): No corrosive esophagitis was induced. Rats were kept under standard laboratory conditions and fed for 28 days with free access to standard pellet food and tap water.

Sample Collection: At the end of the 28-day study period, all rats were euthanized with high-dose anesthetics. A 20 mm-long section of esophageal tissue was removed for histological evaluation. The proximal section of the burnt segment was placed in 10% neutral formaldehyde for histological examination and stored under appropriate conditions until the assay.

Histopathological evaluation

Routine histological methods were applied to tissues fixed in neutral formaldehyde. Four micrometer-thick slices were cut from the tissue embedded in paraffin blocks and stained with hematoxylin and eosin [12].

Stenosis Index (SI): The stenosis index (SI) has been used to determine stricture severity in hollow organs, especially the esophagus. The esophageal wall thickness is measured in two random areas each from 4 separate regions with an ocular micrometer using a scanning lens of 4 x 10 magnification on a light microscope (Olympus BX51, Tokyo, Japan), the average of which is calculated to evaluate SI along with the lumen diameters (Figure 1) (A_{av}=[A1+A2]/2). The lumen width is also measured from two separate areas with two separate lines, and the average is calculated (B_{av}=[B1+B2]/2). SI is finally calculated as average wall thickness divided by average lumen diameter (SI = A_{av}/B_{av}) [13,14].

Tissue damage classification

Submucosal collagen intensity, damage within the muscularis mucosa, and collagen density in the tunica muscularis were evaluated with scoring in three distinct categories. Submucosa is evaluated as 0: no damage, 1: mild, and 2: severe damage. Damage in the muscularis mucosa is scored as 0: absent and 1: present. The tunica muscularis was evaluated as 0: no damage, 1: mild and 2: severe damage. These points were summed up to get a score from 0 to 5 (Figure 2) [15].

Statistical analysis

Statistical analyses were performed using NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA). Descriptive statistical methods were used (mean, standard deviation, median, frequency, percentage, minimum, maximum values) in the evaluation of quantitative data, and Kruskal Wallis test was used in the comparison of more than 3 non-normally distributed groups. To determine the origin of the difference and compare two groups, Mann Whitney U test was used. Statistical significance was set at the levels of P <0.01 and P <0.05.

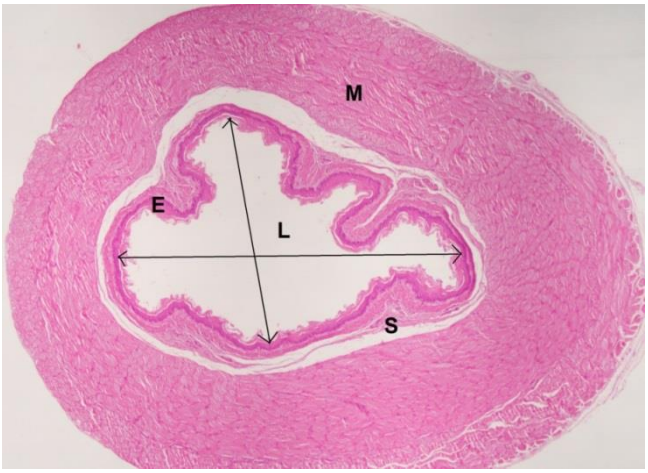

Figure 1: Normal histology of transverse esophageal section in control group (Double arrow depicts lumen width. Lumen (L), epithelium (E), submucosa (S), tunica muscularis (M) (Hematoxylin and eosin ×40))

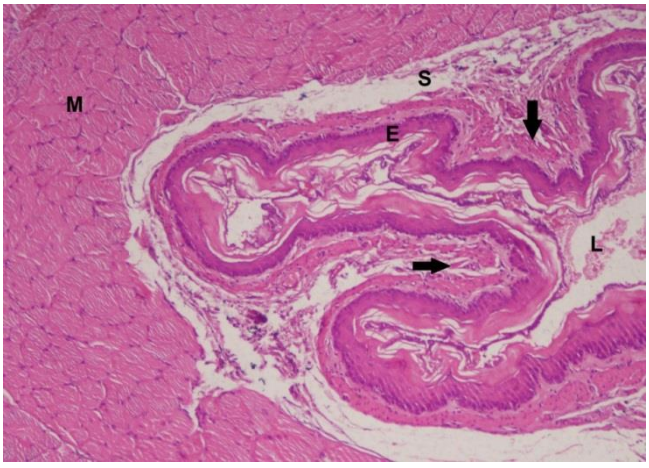

Figure 2: Histology of transverse esophageal section in untreated corrosive burn group (Lumen (L), epithelium (E), submucosa (S), tunica muscularis (M), collagen deposition and inflammation (arrows) (Hematoxylin and eosin ×100))

Results

Tissue Damage (TD) scoring results

A normal histological structure was observed in the morphological images of the control group's slices. In the histological slices of Group 1 (esophageal corrosive burn and no treatment), evident degenerative changes were observed: A significant increase was detected in submucosal collagen as well as collagen deposited around circular muscle fibers in the inner muscular layer. Also, the muscle fibers in the muscularis mucosa were significantly more irregular and degenerate.

All the groups were scored histopathologically and results were statistically compared (Table 1). As the tissue damage (TD) score of Group 4 was 0, it was not included in the evaluation in Table 1.

A statistically significant difference was found between the TD scores of the groups (P=0.005). Evaluations were made to determine from which group the significance originated. A statistically significant difference was determined between Groups 1 and 2 (P=0.001).

The difference between Groups 1 and 3 was not statistically significant (P=0.139).

The comparison of Groups 2 and 3 revealed that there were significant differences between honey and prednisolone in protecting against the development of esophageal stricture (P=0.045).

Stenosis Index (SI) scoring results

The stenosis index (SI) results and statistical comparisons are shown in Table 2.

A statistically significant difference was determined between Groups 2 and 3 with respect to the SI results (P=0.003), and between Groups 4, 1 and 3 (P=0.001, P=0.002, respectively) in terms of mean SI scores. Compared to the control group, the scores of Groups 1 and 3 were significantly low, and that of Groups 2 and 4 were similar (P=0.674).

Table 1: Comparisons of the tissue damage scores

Tissue Damage Score	Mean (SD)	Min-Max	Median	*P*-value
Group 1 (burn)	3.50(0.92)	2–5	3.5	[a]0.005*
Group 2 (burn + honey)	1.00(0.92)	0–3	1	
Group 3 (burn+prednisolone)	2.38(1.51)	0–4	3	
Group 1(burn)	3.50(0.92)	2–5	3.5	[b]0.001**
Group 2 (burn + honey)	1.00(0.92)	0–3	1	
Group 1 (burn)	3.50(0.92)	2–5	3.5	[b]0.139
Group 3 (burn+prednisolone)	2.38(1.51)	0–4	3	
Group 2 (burn + honey)	1.00(0.92)	0–3	1	[b]0.045*
Group 3 (burn+prednisolone)	2.38(1.51)	0–4	3	

[a]Kruskal Wallis Test, [b]Mann Whitney U test, ** P<0.001, * P<0.05

Table 2: Comparisons of the histopathological stenosis index

Histopathological Stenosis Index	Mean (SD)	Min-Max	Median	*P*-value
Group 1 (burn)	7.77(2.56)	5.5–13.6	7.25	[a]0.001**
Group 2 (burn + honey)	4.19(0.63)	3.2–5.4	4.1	
Group 3 (burn+prednisolone)	6.09(1.23)	4.9–8.4	5.7	
Group 4 (control)	4.06(0.64)	2.9–5.08	4.07	
Group 1 (burn)	7.778(2.56)	5.5–13.6	7.25	[b]0.001**
Group 2 (burn + honey)	4.19(0.63)	3.2–5.4	4.1	
Group 1 (burn)	7.77(2.56)	5.5–13.6	7.2	[b]0.059
Group 3 (burn+prednisolone)	6.09(1.23)	4.9–8.4	5.7	
Group 1 (burn)	7.77(2.56)	5.5–13.6	7.25	[b]0.001**
Group 4 (control)	4.06(0.64)	2.9–5.08	4.07	
Group 2 (burn + honey)	4.19(0.63)	3.2–5.4	4.1	[b]0.003*
Group 3 (burn+prednisolone)	6.09(1.23)	4.9–8.4	5.7	
Group 2 (burn + honey)	4.19(0.63)	3.2–5.4	4.1	[b]0.647
Group 4 (control)	4.06(0.64)	2.9–5.08	4.07	
Group 3 (burn+prednisolone)	6.09(1.239	4.9–8.4	5.7	[b]0.002*
Group 4 (control)	4.06(0.64)	2.9–5.08	4.07	

[a]Kruskal Wallis Test, [b]Mann Whitney U test, ** P<0.001, * P<0.05

Discussion

The results of this study showed that in the treatment of esophagitis associated with caustic substances, honey was more successful than prednisolone in decreasing stricture development and reducing TD to a minimum.

Exposure to caustic substances is still a fundamental problem in undeveloped regions of the world [16,17]. Liquefaction necrosis occurs in the esophageal mucosa with the ingestion of alkaline agents. Free oxygen radicals are known to increase with ischemia and TD around these areas, which trigger

lipid peroxidation in intracellular organellar membranes. This continues with an increase in membrane permeability and thereby, an increase in leukocytes starts the inflammatory process, escalating the damage.

In mild cases, esophageal functions can be regained. However, severe cases can result in stricture formation. Several experimental studies have been conducted with the aim of preventing stricture development, with treatments including agents that prevent lipid peroxidase inhibition such as tumor necrosis factor (TNF)-alpha antibodies, ozone therapy, sucralfate, pentoxifylline, and ketotifen [18,19].

The use of corticosteroids to prevent esophageal stricture development after the ingestion of corrosive materials is controversial. Some studies have reported the use of corticosteroids as 0%–25% in first- and second-degree esophageal burns and that stricture developed in 88% of cases when they are not used [19,20]. According to the results of some studies, the use of corticosteroids is of no benefit, and it has been suggested that stricture develops at rates of 20% to 38% despite the selected treatment for esophageal burns [21-23].

In the current experimental study, no statistically significant differences were determined between the prednisolone group (Group 3) and the esophagitis group irrigated with saline only (Group 1) with respect to the SI and TD scores. Prednisolone did not show a protective effect against fibrosis and stricture formation by reducing tissue damage.

According to the comparisons of the histopathological TD scores of Groups 2 and 3 (burn +honey and burn + prednisolone, respectively), honey showed a significantly greater histopathological effect in preventing fibrosis and stricture formation compared to prednisolone.

Honey is used as a strong agent in wound healing due to its anti-bacterial and anti-inflammatory effects [24-26]. Acceleration of epithelialization is necessary for wound healing. It is possible to reduce the inflammation, edema, and exudation formation in the wound with honey [24,27].

Clinical and animal studies have shown that honey reduces gastric acid expression. Honey added to the daily diet has been used to treat gastric ulcers. In a previous study of 600 gastric ulcer patients, it was reported that approximately 80% were treated with oral honey supplementation, and 59% of the patients taking honey recovered from ulcers [28].

Honey has also been proven effective in the treatment of patients with benign oral ulcers [29,30]. In a study of 50 adults with minor oral ulcers by Mohamed and Al-Dour, the ulcers recovered in three days in the group receiving honey, while this improvement was not seen in the control group [29].

In general, the advantages of filling a wet wound or abscess pits with honey are known. This is primarily because the mechanical form of honey forms a chemical barrier thus preventing cross-infection. It also accelerates adaptation of a tissue flap and shortens treatment time. The efficacy of honey against some strains of Pseudomonas and Staphylococcus has been shown to be superior to some antibacterial agents [30].

The chemical debridement property of honey has been reported to have great advantages in Fournier gangrene and decubitus ulcers. A previous clinical study compared 50 patients using Savlon antiseptic and honey. Recovery was seen in 60% of the wounds cleaned with honey and in 36% of those cleaned with antiseptic in the same period [26].

Limitations

This experimental research has some limitations. As with all animal experiments, it is imperative to work with a limited number of animals. In addition, our study evaluated the histopathological results only. Since the rats were sacrificed shortly after, we could not examine the esophageal pathologies that may occur in the long term.

Conclusion

The results of this experimental study showed that compared to prednisolone, the effects of honey in preventing stricture and fibrosis formation were histopathologically and significantly greater. Honey can be used in emergency departments, especially for children. Further clinical studies are required to assess honey in the acute treatment of corrosive burns.

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