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The Healing Effect of Resveratrol and Platelet Rich Plasma in Corrosive Esophagitis Model in Rats

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Research Article

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ABSTRACT

Background: Corrosive esophageal burns have high morbidity and mortality. The effective treatment is controversial. In our study, we aimed to examine the effects of resveratrol (RSV) and platelet rich plasma (PRP) on healing in the corrosive esophagitis model in rats.

Material and methods: A total of 24 rats were randomly divided into 4 groups each as esophagitis, control, PRP and RSV groups. No treatment was administered to the control group. The esophagitis model was induced in the esophagitis and treatment groups. The esophagitis group was not treated. PRP group was treated with PRP, RSV group was treated with RSV. Pathological and biochemical examinations were performed from distal esophagitis.

Results: The highest tissue IL-1, IL-6, and TNF-α levels were observed in the esophagitis group. The lowest tissue IL-1, IL-6, and TNF-α levels were noted in the control group. The highest tissue TAS levels were observed in the control group. The lowest tissue TAS levels were noted in the esophagitis group. The other groups had significantly lower mean tissue TOS and OSI levels than the esophagitis group ($P<0.05$).

Conclusions: PRP and RSV have a healing effect on esophagitis. We are of the opinion that it may be included in clinical practice over time if the dose and duration of treatment can be adjusted better for RSV.

Keywords: Antioxidant, esophagitis, oxidant, platelet rich plasma, resveratrol.

Sıçanlarda Korozif Özofajit Modelinde Resveratrol ve Trombositten Zengin Plazmanın İyileştirici Etkisi

Süreç

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ÖZ

Giriş: Korozif özofagus yanıkları yüksek morbidite ve mortaliteye sahiptir. Etkili tedavi tartışmalıdır. Çalışmamızda sıçanlarda koroziv özofajit modelinde resveratrol (RSV) ve trombositten zengin plazmanın (PRP) iyileşme üzerine etkilerini incelemeyi amaçladık.

Materyal ve metod: Toplam 24 rat rastgele olarak özofajit, kontrol, PRP ve RSV grupları olmak üzere 4 gruba ayrıldı. Kontrol grubuna herhangi bir tedavi uygulanmadı. Özofajit modeli, özofajit ve tedavi gruplarında oluşturuldu. Özofajit grubu tedavi edilmedi. PRP grubu PRP ile tedavi edildi, RSV grubu RSV ile tedavi edildi. Distal özofajitten patolojik ve biyokimyasal incelemeler yapıldı.

Bulgular: En yüksek doku IL-1, IL-6 ve TNF-α seviyeleri özofajit grubunda gözlendi. En düşük doku IL-1, IL-6 ve TNF-α seviyeleri kontrol grubunda kaydedildi. En yüksek doku TAS seviyeleri kontrol grubunda gözlendi. En düşük doku TAS seviyeleri özofajit grubunda kaydedildi. Diğer gruplar, özofajit grubuna göre anlamlı olarak daha düşük ortalama doku TOS ve OSI seviyelerine sahipti ($P<0.05$).

Sonuç: PRP ve RSV'nin özofajit üzerinde iyileştirici etkisi vardır. RSV için doz ve tedavi süresi daha iyi ayarlanabilirse zamanla klinik pratiğe dahil edilebileceği kanaatindeyiz.

Anahtar sözcükler: Antioksidan, özofajit, oksidan, trombositten zengin plazma, resveratrol

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Introduction

The destruction of the esophagus after ingestion of caustic substances is defined as corrosive esophagitis. The development of corrosive esophagitis may present with different complications in the acute and chronic periods. While an acute pathology such as the development of perforation requires emergency surgery, the development of structure will be in the chronic period. Balloon dilatation or endoscopic stenting may be required to treat the structure. Treatment of esophageal injuries is as risky as the injury.

Caustic substances are products that exist in our lives such as cleaning materials and sink openers that we always use. It can be acidic or basic. Due to its clear appearance, most caustic substances may be mistaken for water by children. Children may accidentally ingest caustic substance. Cases are frequently seen in children under 5 years of age. Adults generally use caustic substances for suicidal purposes [1]. Suicidal uses cause serious damage to the esophagus as there will be more intake.

The development of corrosive esophagitis is among the life-threatening, serious causes of morbidity and mortality. For this reason, it is a situation that needs improvement in terms of emergency treatment, palliative approach, elective operations, and treatment. Only interventional approaches are not considered appropriate. A very meticulous treatment algorithm should be created. In this algorithm, medical approaches have been given great importance in the literature and it has been found worthy of research. Esophagitis is basically a tissue destruction that develops under inflammation and oxidative stress. It is known that the use of basic substances, in particular, causes more mucosal irritation [2]. In studies, we see that anti-inflammatory and antioxidant drugs have been tried to neutralize the effects of inflammation and oxidative stress [3].

In this study, we aimed to show the effect of Prp and RSV, which had previously shown anti-inflammatory and antioxidant properties, on the healing of esophagitis in the experimental corrosive esophagitis model, which we prepared using an alkaline substance.

Material And Methods

Ethical Approval

Our experimental study was approved by Kırıkkale University Animal Experiments Local Ethics Committee on September 2, 2020 with the number 2020/04-22.

Animals

The corrosive esophagitis model was prepared according to the model described by Gehanno et al. [4]. A total of 24 wistar albino male rats weighing 220-260 g were randomly divided into 4 groups of 6 animals each as esophagitis, control, PRP and RSV groups. Additionally, 5 rats of the same species and weight were used to obtain PRP. All rats included in the study were placed in independent cages of equal size and fed with standard chow and tap water. The rats were kept in a soundproofed room with a 12 hour light/dark cycle at 23±1°C room temperature and 55±5% humidity. The experiment was carried out between 08:30 and 16:30, and the light and sound level of the experimental environment was kept under constant control. Rats were fasted at least 8 hours before the procedure.

PRP Preparation

For PRP preparation, five rats of the same weight and the same species were used. Cardiac blood from rats narcotized under anesthesia was taken into 3.2% sodium citrate (Merck, Darmstadt, Germany) tubes with a blood/citrate ratio of 9/1. Collected blood was centrifuged for 10 minutes at 400×g. The upper portion was further centrifuged for 10 minutes at 800×g. The upper 2/3 portion was discarded. The lower 1/3 portion was considered PRP [5]. PRP was kept in a freezer under –20°C until it was used.

Anesthesia and Surgery

No treatment was administered to the control group. The esophagitis model was induced in the esophagitis and treatment groups. All animals were anesthetized by administering ketamine 8 mg/body weight (kg) intramuscularly for the experimental esophagitis procedure. After the midline incision, the distal esophagus was clamped and 0.1 ml of 37.5% NaOH was administered. It was aspirated after 90 seconds and the inside of the esophagus was irrigated with saline [6]. The esophagitis group was not treated. The PRP group received 7 days of PRP treatment at a dose of 0.5 mL/kg/day by oral gavage. The RSV group received 7 days of RSV (Interpharma Praha, Tokyo, Japan) treatment at a dose of 10 mg/kg/day by oral gavage [7]. The experiment was ended on day 8, and the rats in all groups were sacrificed by decapitation (cervical dislocation). The distal esophagus tissue of 0.5 cm length subjected to the procedure was longitudinally divided into two, and IL1, IL6, TNF alpha, TAS (Total Antioxidant Status) and TOS (Total Oxidant Status) were biochemically analyzed from the half of the tissue. The other half was histopathologically examined.

Tissue homogenization

For this study, esophageal samples were collected from 24 rats. Tissue samples were stored at -80°C until the experiments. Tissue samples were homogenized with PBS (Phosphate Buffer Saline, pH: 7.4) by using a homogenizer (Fast prep-24, MP Biomedical, USA).

Macroscopic evaluation of esophagus

The materials of the excised esophageal tissue were defixed in 10% neutral-buffered formalin. All the

samples sliced longitudinally were followed up for 1 night for histopathological examination.

Histopathologic evaluation of esophagus

After the tissues were embedded in paraffin blocks, they were cut at a thickness of 4 micrometers and stained with hematoxylin and eosin (H&E) following deparaffinization and rehydration. Histopathological findings were evaluated under a light microscope by a pathologist who was blinded to the experimental groups. Inflammation was defined as the infiltration of neutrophils and eosinophils in the esophageal tissue. Stricture was defined as an increased amount of collagen in the subepithelial tissue. Histopathological scoring of the esophageal injury was made according to the highest area and degrees determined (Esophageal injury scoring: 0: normal tissue, 1: the presence of inflammation and stricture in mucosa and submucosa, 2: the presence of inflammation and stricture in tunica muscularis, 3: the presence of inflammation and stricture in all three layers, 4: the presence of necrosis).

Statistical analysis

Statistical Package for Social Sciences version 21.0 software for Windows (IBM SPSS Statistics for Windows, Version 21.0 Armonk, NY: IBM Corp., USA) was used for the statistical analyses of the study. The assumption of normality was tested by the Shapiro-Wilk tests. Normally distributed data were compared with one-way ANOVA, followed by a Tukey correction test (post hoc). Non-normally distributed data were analyzed using the Kruskal-Wallis test, followed by the games-havell correction test. A p-value below 0.05 was considered statistically significant.

Results

For the evaluation of oxidation and biochemical evaluation was performed as Özden et al. [8] *Table 1* shows the evaluation of tissue biochemical and histopathologic results in detail. The highest tissue IL-1, IL-6 and TNF-α levels were observed in esophagitis group animals. The lowest tissue IL-1, IL-6, and TNF-α levels were noted in the control group. The other groups had significantly lower mean tissue IL-1 levels than the esophagitis group (P<0.05). There was also a significant difference between the control and RSV groups in mean tissue IL-1 (P<0.05). However, there was no significant difference between the control and PRP groups (P=0.54). There was also a significant difference between the PRP and RSV groups in mean tissue IL-1 (P<0.05). It was found that PRP decreased IL-1 level more significantly. In the tissue IL-6 evaluation, the esophagitis group had significantly higher IL-6 levels than the other groups (P<0.05). There was also a significant difference between control and RSV groups/PRP and RSV groups (P<0.05). However, there was no significant difference between the control and PRP groups (P=0.98). We found that PRP application significantly decreased IL-6 level compared to RSV. Similar to other conclusions, the esophagitis group had significantly higher TNF-alpha levels than the other groups (P<0.05). There was also a significant difference between control and RSV groups/PRP and RSV groups (P<0.05). However, there was no significant difference between the control and PRP groups (P=0.63). The IL-1, IL-6 and TNF alpha results yielded similar statistical results. As is seen, the RSV group results were significant compared to the esophagitis group. An improvement was observed in the values of esophagitis tissue treated with RSV. However, the values obtained were not at a level to be considered significant compared to normal esophageal tissue or PRP.

The highest tissue TAS levels were observed in the control group. The lowest tissue TAS levels were noted in the esophagitis group. The other groups had significantly higher mean tissue TAS levels than the esophagitis group (P<0.05). There was also a significant difference between the control and PRP groups/control and RSV groups (P<0.05). However, there was no significant difference between the PRP and RSV groups (P=0.96). We found that PRP and RSV were equally effective at the antioxidant level. The other groups had significantly lower mean tissue TOS and OSI levels than the esophagitis group (P<0.05). There was no significant difference between the control, PRP and RSV groups in TOS and OSI levels.

Table 1. The evaluation of tissue biochemical and histopathologic results of the study groups

Variables	Esophagitis group	Control group	PRP group	RSV group
IL1	1540.45±194.60 [a,b,c]	728.46±104.59 [a,e]	793.64±87.04 [b,f]	1138.74±132.22 [c,e,f]
IL6	177.90±11.74 [a,b,c]	84.28±9.63 [a,e]	85.71±7.16 [b,f]	126.80±10.26 [c,e,f]
TNF	169.26±11.74 [a,b,c]	75.64±10.13 [a,e]	80.82±8.50 [b,f]	111±10.59 [c,e,f]
TAS	1.01±0.06 [a,b,c]	3.01±0.08 [a,d,e]	2.02±0.75 [b,d]	1.85±0.86 [c,e]
TOS	20.22±1.39 [a,b,c]	9.61±0.57 [a]	10.11±3.03 [b]	10.28±1.01 [c]
OSİ	20.06±2.31[a,b,c]	3.32±0.28 [a]	6.06±3.49 [b]	7.66±3.80 [c]
His. Patho.	1.62±.0.51[a]	0.00±0.00 [a,d,e]	1.25±0.46 [d]	1.50±0.53 [e]

Values are presented as median (interquartile range). Kruskal-Wallis test, a) The difference between group I and group II were statistically significant (P<0.01), b) The difference between group I and group III were statistically significant (P<0.001), c) The difference between group I and group IV were statistically significant (P<0.01), d) The difference between group II and group III were statistically significant (P<0.05), e) The difference between group II and group IV were statistically significant (P=0.005) f). The difference between group III and group IV were statistically significant (P<0.05)

In the evaluation of histopathological results; there was a significant difference between the tissue scores of the control group and the other groups (P<0.05). There was no significant difference between the esophagitis group and the treatment groups (P=0.044, P=0.96, respectively). There was also no significant difference between the PRP and RSV groups (P=0.75). Although better histopathological data were obtained in the treatment groups, there was no significant improvement. In the histopathological evaluation of the groups, some slides were illustrated in *Fig. 1,2,3*.

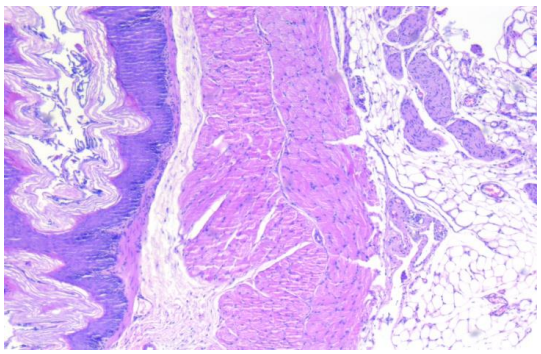

Fig 1. The usual full-thickness histological appearance of the esophagus of the control group rat (H&E, X50)

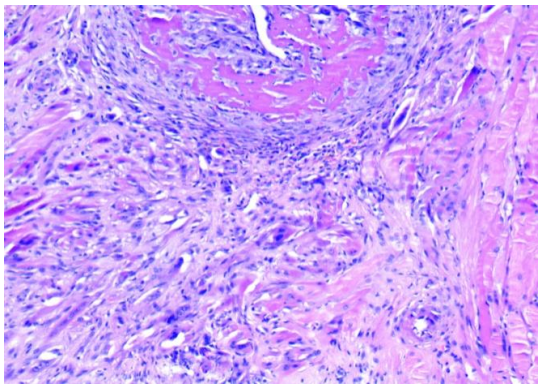

Fig 2. Esophagitis group; significant fibroblastic proliferation, mixed inflammatory cell infiltration in the esophageal muscle layer treated with corrosive agents (H&E, X100)

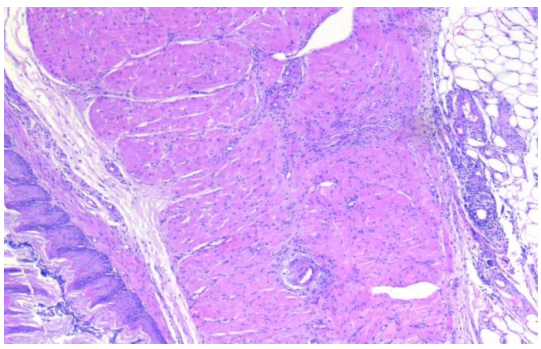

Fig 3. Mild chronic inflammation in muscle layer and adventitia in RSV-treated rat after esophagitis (H&E, X50)

Discussion

Caustic substances are generally cleaning products used in homes and workplaces. Caustic substance exposure usually occurs in children after accidental ingestion. The child is usually exposed to this substance in a small amount, as the taste is disturbing or the ability to swallow is not practical enough. Esophageal injury may develop in 20% of children [3]. In adults, it can be used accidentally or for suicidal purpose. If it is used deliberately, a very severe clinical manifestation may occur.

Whether the caustic substance is alkaline or acidic will have different effects. Since an alkaline caustic substance is odorless and tasteless, exposure can be more. An acidic substance can shorten the exposure time by drinking quickly. The severity of the injury is related to the concentration of the substance, the amount ingested, the duration of tissue contact, and the pH of the substance. The local experience in Denmark, Israel, United Kingdom, Peru, Spain, Australia, Saudi Arabia and Turkey has shown that alkaline agents mostly cause caustic injury [9]. NaOH, known as the sink openers, is the most well-known and most used in experimental studies among alkaline agents [10]. Therefore, in our study, we created the esophagitis model using NaOH.

When corrosive esophagitis develops, while erythema, edema, bullae and small ulcers are frequently seen in the superficial injury of the mucosa, deep ulceration and ulcer-related complications can be observed in the case of deeper involvement. Fistula may develop from the esophagus to the trachea. It may cause aortoenteric fistulas and esophageal stricture during ulcer healing period [11]. If esophageal stricture has developed, endoscopic dilatation, stent placement or surgical techniques may be required [12]. Caustic substance can increase the development of esophageal cancer by 1000-3000 times [13].

In a study by Cemil et al. [14] the effect of pentoxifylline, which is known to have anti-inflammatory activity, on healing in an experimental corrosive esophagitis study was evaluated. They found that the use of pentoxifylline alone did not change the esophageal wall thickness and stenosis index, but decreased the tissue hydroxyproline level. In the same study, they obtained more effective results with the combination of pentoxifylline + trimetazidine and recommended combined treatment. Tülin et al. [15] on the other hand, designed a clinical study and investigated the effect of the known antioxidant effect of N-Acetyl Cysteine on the recovery of patients with esophagitis. They discussed many issues in this study. First of all, they said that dilatation with endoscopy causes perforation in the early period, and they used only endoscopy in the follow-up of treatment without dilation in their follow-up algorithms. Apart from this,

they followed their patients under antibiotic therapy, as broad-spectrum antibiotics were used in all open wounds. In addition, they emphasized that they obtained positive results for N-Acetyl Cysteine and decreased oxidative values. Mesenchymal stem cell therapy, whose anti-inflammatory and antioxidant effects have been shown in previous studies, has also been tested in esophagitis models [16,17]. As in these studies, many substances have been investigated in terms of their effects on the healing of corrosive esophagitis. Examples of these are methylene blue, polaprezinc, garlic (Allium sativum) oil, or platelet rich plasma [18-21]. The common aspect of all these substances is that they have anti-inflammatory and antioxidant effects. Cevik et al. [22] found that increased oxidative stress was associated with esophageal burns and injury. Free oxygen radicals are known to cause many pathological disorders [23].

When the literature is scanned, we see a lot of medical treatment trials for the treatment of corrosive esophagitis. This is because surgery may be unnecessary in the early period and may also be very mortal. Balloon dilatation, on the other hand, is not used since it carries a risk of perforation in the active period and significant stricture findings are not fully developed. Inflammatory changes detected in the early period and increasing oxidative data indicate that medical treatment will be beneficial. Of course, a fully effective treatment has not yet taken its place in use. Among the current treatment protocols, there is no clear treatment algorithm other than steroids, broad-spectrum antibiotics or medical applications for the neutralization of caustic agents. Experimental studies focused mostly on anti-inflammatory and antioxidant agents. It is aimed to find the most active substance and take its place in the treatment [24,25].

In the light of all these data, we wanted to examine the effect of suppression of inflammation and oxidative stress on the treatment in the experimental corrosive esophagitis model study. For this purpose, we aimed to show the effect of Prp and RSV, which have shown anti-inflammatory and antioxidant properties in previous studies, on healing of esophagitis.

PRP is an autologous plasma preparation richer in platelets than whole blood in terms of concentration [26]. There are many studies on the antioxidant and anti-inflammatory properties of PRP, and it has been added to treatment protocols in many areas today. Especially successful results have been achieved in musculoskeletal treatments [27]. The healing effects of PRP in corrosive esophagitis have been studied in previous studies [28]. Kim et al. [29] reported that topical application of PRP significantly increased the reepithelialization process in ulcers. We preferred topical application for the same reason and because we wanted to carry out biochemical and histopathological analysis of tissue.

Studies have been conducted on the anti-inflammatory and antioxidant properties of resveratrol, which is found in nutrients such as grapes, strawberries and peanuts, and positive results have been achieved. Many studies have shown its various benefits such as protective action for neurodegeneration, diabetes and its complications, anti-cancer and anti-aging activity [30]. It was emphasized in a study that resveratrol had been used since ancient times and is the same as the historical drug known as *"kojo-kon"* in Chinese and Japanese culture [31]. We aimed to examine the efficacy of resveratrol in the treatment of esophagitis, considering that this historical drug, which can be added to daily life as a food supplement and is easily available today, should be included in the studies and investigated.

In our experimental esophagitis model, we used alkaline NaOH. We obtained IL-1, IL-6 and TNF-α levels as an indicator of inflammation and TAS, TOS and OSI levels as an oxidation indicator in the esophagitis group compared to the control group. These results have proved us that NaOH causes esophagitis. The significant improvement in biochemical parameters (inflammation and oxidation markers) obtained from the RSV and PRP groups that we created as treatment groups compared to the esophagitis group and the values close to normal mucosal structure have demonstrated the therapeutic effect of RSV and PRP. When the RSV and PRP scores were evaluated in detail and compared with each other, it was observed that PRP yielded superior results compared to RSV. Of course, this may be related to dose adjustment and duration of treatment. Similarly, the histopathological evaluation showed an improvement in the PRP and RSV groups. However, it should be evaluated for histopathological improvement with a longer-term study.

In conclusion, when the data we obtained were analyzed, we found that PRP was therapeutic in line with the literature. We observed that RSV corrected the biochemical values in the tissue almost equivalent to PRP. We believe that resveratrol, which has known anti-inflammatory and antioxidant activity and can be obtained from daily foods since ancient times, may take place in the treatment of esophagitis. Of course, larger studies are needed.

Study Limitations

In the experimental corrosive esophagitis experiment, a longer wait was required for the development of the structure. Our study did not allow us to obtain sufficient data to show the histopathological changes.

Availability of Data and Materials

If necessary, data will be provided from the corresponding author (HÖ).

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Conflict of Interest

There is no conflict of interest, and that all authors have read and approved of the manuscript been submitted.

Authors' Contributions

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors

HÖ: work management, article writing, experimental procedure follow-up, MG: design, article writing, literature review, YŞ: experimental procedure follow-up, GK: design, article writing, literature review, statistics, HB: biochemical analysis, AK: pathological analysis

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