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Deneysel Akut Respiratuar Distres Modelinde Dekspantenol'ün Anti-İnflamatuvar ve Antioksidan Etkilerinin Araştırılması

Anti-Inflammatory and Antioxidant Effects of Dexpantenol on the Experimental Acute Respiratory Distress Model

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ÖZET

Amaç: Akut respiratuar distres sendromu (ARDS) pulmoner veya ekstrapulmoner nedenlerle gelişerek, akciğerlerde ciddi fonksiyon kaybına veya mortaliteye neden olabilen bir klinik sendromdur. Dekspantenol antioksidan ve anti-inflamatuar etkilere sahip önemli bir tedavi edici ajandır. Materyal-Metod: Çalışmada oleik asit kullanılarak oluşturulan akut respiratuar distres modelinde dekspantenol'ün anti-inflamatuvar ve antioksidan özellikleri değerlendirilmiştir. Bu amaç doğrultusunda 50 dişi Wistar-albino rat beş gruba ayrıldı (n: 10). Gruplar Control (C), Oleik asit (O), Dekspantenol+Oleik asit (DO), Dekspantenol+Oleik asit+Despantenol (DOD) ve Oleik asit+Dekspantenol (OD) olarak adlandırıldı. Sıçanlar sakrifiye edildikten sonra serum örneklerindeki interlökin-1α ile Tümör Nekroz Faktör alfa düzeyleri belirlenmiştir. Akciğer dokusunda ise ışık mikroskobu ile histopatolojik inceleme ve malondialdehid doku, glutatyon peroksidaz, katalaz enzim aktivite düzeyleri ölçümleri yapılmıştır. Bulgular: Elde edilen sonuçlar, oleik asit verilerek tedavi uygulanmamış grupta histopatolojik olarak anlamlı düzeyde akut akciğer hasarı tespit edilmiştir. Doku örneklerine yapılan biyokimyasal analizler histopatolojik sonuçları desteklemektedir. Tedavi gruplarından elde edilen sonuçlar, oleik asidin neden olduğu hasarın dekspantenol tedavisi ile birlikte azaldığını göstermektedir. Özellikle oleik asit uygulanan gruplarda meydana gelen MDA düzeylerindeki artış ve tedavi gruplarında ki azalma ile antioksidan parametrelerdeki artış, oksidatif hasarın etkisini göstermektedir.Sonuçlar: Sonuç olarak dekspantenol uygulamasının deneysel akut respiratuar distres sendromu gelişimini önlemede etkili olduğu, bu etkinin dekspantenolun anti-inflamatuvar ve antioksidan özellikleri sayesinde olduğunu düşünülmektedir.

Anahtar Kelimeler: Akut akciğer hasarı, Anti-inflamatuar, Antioksidan, Dekspantenol, Oleik asit

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ABSTRACT

Objective: Acute respiratory distress syndrome (ARDS) is a clinical syndrome that can develop due to pulmonary or extrapulmonary causes, causing serious loss of function or mortality in the lungs. Dexpanthenol is an important therapeutic agent with antioxidant and anti-inflammatory effects. In the study, anti-inflammatory and antioxidant properties of dexpanthenol were evaluated in the acute respiratory distress model created using oleic acid. Material and Method: For this purpose, 50 female Wistar-albino rats were divided into five groups (n:10). The groups were named as Control (C), Oleic acid (O), Dexpanthenol+Oleic acid (DO), Dexpanthenol+Oleic acid+Despanthenol (DOD) and Oleic acid+Dexpanthenol (OD). After the rats were sacrificed, levels of interleukin-1α and Tumor Necrosis Factor-alpha in serum samples were determined. In the lung tissue, histopathological examination and measurements of malondialdehyde tissue, glutathione peroxidase, catalase enzyme activity levels were made with light microscopy. Results: The results obtained showed that histopathologically significant acute lung injury was detected in the group that was not treated with oleic acid. Biochemical analyzes performed on tissue samples support histopathological results. Results from treatment groups show that the damage caused by oleic acid decreases with dexpanthenol treatment. Especially MDA levels as oxidative parameter and CAT and GSH levels as antioxidant parameters show the effect of oxidative damage.Conclusions: In conclusion, it is thought that the application of dexpanthenol is effective in preventing the development of experimental acute respiratory distress syndrome, and this effect is due to the anti-inflammatory and antioxidant properties of dexpanthenol.

Keywords: Acute lung injury, Anti-inflammatory, Antioxidant, Dexpanthenol, Oleic acid

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1. INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a widespread, devastating clinical syndrome with high mortality and a severe loss of function in the lungs due to local or systemic inflammatory response, developing due to pulmonary or extrapulmonary causes (1,2). Acute lung injury (ALI) and ARDS constitute a group of diseases commonly defined as "acute non-cardiogenic edematous lung injury". Diseases such as ALI and ARDS constitute 30-50% of death rates in intensive care units (3). Many pathogenic conditions such as sepsis and pneumonia can trigger ARDS (4).
Although it has been 51 years since it was first described in 1967 and intensive studies have been carried out on it especially in the last 20 years, there is no specific and effective pharmacological intervention for ARDS (5). Therefore, ARDS is encountered frequently and has a high mortality rate. In recent years, the improvement of practices in intensive care units and the positive results of mechanical ventilation used to reduce lung damage in ARDS treatment have led to a decrease in ARDS mortality (6,7). Various methods have been described in the literature that can be applied to laboratory animals for studies on ALI/ARDS disease. The acute and repair phase of lung injury induced by oleic acid in rats has a histological and physiological appearance similar to human ARDS (8).
In studies, Dexpanthenol has been used systemically in corneal or conjunctival lesions of the eye for topical use as an adjuvant in mucosal lesions in the nose (9) and to decrease bowel tone after surgery and to worsen peristaltic movements (10). Although many studies have been conducted on the antioxidant and anti-inflammatory effects of dexpanthenol, no study has been found to investigate the effects on ARDS induced by oleic acid in rats. In light of this information, the primary aim of the study is to examine the effect of dexpanthenol on lung damage in rats with ARDS induced by oleic acid. The secondary purpose is to show that the anti-oxidant feature plays a role in the possible protective effect of dexpanthenol in ARDS. This study aims to determine and compare the levels of lipid peroxidation, antioxidant enzyme levels, pro-inflammatory and anti-inflammatory levels, which are indicators of oxidative damage in tissues when ARDS is induced in groups with and without dexpanthenol.

2. MATERIAL AND METHODS

Experimental Animal Material

All animal experiments were carried out under optimized laboratory conditions using a total of 50 female Wistar-albino rats weighing between 250-300 g in the XXX Experimental Animals unit. Analyzes of the experiment were carried out in XXX Central Research Laboratory and Faculty of Medicine Histology-Embryology and Physiology Department Laboratory.

Experimental Groups and Application Protocol

In this study, 50 female Wistar-albino rats (250-300 g) were used. Five groups were formed with ten rats in each group. Before the study began, all rats were weighed and groups were named as follows:

Control group (C): 100 mg/kg saline was administered intravenously (iv) using the tail vein, 30 minutes after injection, saline was given intraperitoneally (ip) in the same volume as Dexpanthenol. After four hours the animals were sacrificed.
Oleic acid group (O): 100 mg/kg oleic acid was given iv via the tail vein, 30 minutes after oleic acid injection, the same volume of dexpanthenol was given intraperitoneally, animals were sacrificed after 4 hours.
Dexpanthenol + Oleic acid group (DO): 500 mg/kg dexpanthenol was given up for 7 days and at the end of the 7th day, 100 mg/kg oleic acid was given iv via the tail vein. 30 minutes after the injection, 500 mg/kg ip of physiological saline was given. Animals were sacrificed 4 hours later.
Dexpanthenol + Oleic acid + Despanthenol group (DOD): 500 mg/kg dexpanthenol was given ip for 7 days and at the end of the 7th day 100 mg/kg oleic acid was given iv via the tail vein. Dexpanthenol was given 500 mg/kg ip 30 minutes after the injection. Animals were sacrificed 4 hours later.
Oleic acid + Dexpanthenol group (OD): 100 mg/kg oleic acid was given iv via the tail vein. Dexpanthenol was given 500 mg/kg ip 30 minutes after the injection. Animals were sacrificed 4 hours later.

Acute lung injury was created by administering oleic acid (cis-9-octadecenoic acid; Sigma-Aldrich Germany) at a dose of 100 mg/kg intravenously. Oleic acid; After dissolving in ethanol, 0.9% NaCl was added to the solution and diluted to a concentration of 25 mg/ml. The prepared solution was infused intravenously by placing 24G branules through the tail vein. Intraperitoneal injections were made 30 minutes after intravenous injections, and after 4 hours, intracardiac blood was completely removed under ketamine (50 mg/kg) and xylazine (5 mg/kg) anesthesia, and the animals were sacrificed.
Blood samples were centrifuged at 3000 rpm for 10 minutes for biochemical analysis and the sera obtained were transferred to Eppendorf tubes and stored at -80 ˚C until analysis. Lungs were removed by separating from surrounding tissues. Tissues were fixed with 10% formaldehyde. Lung tissues of rats in the control and experimental groups in the laboratory were removed. Tissues were weighed and individually homogenized with a tissue homogenizer (Ultra Turrax, IKA-WERKE, Germany).
In the lung tissue, the indicator of lipid peroxidation, malondialdehyde (MDA), glutathione peroxidase (GPH-Px) enzyme activities, catalase (CAT) was determined. Interleukin-1 Alpha (IL1-α) and tumor necrosis factor-alpha (TNF-α) parameters from Blood Serums Rat Elisa Kits (Boster antibody and ELISA experts IL1-α Elisa Kit Cat. No: EK0390, Boster antibody and ELISA experts TNF- α Elisa Kit Cat. No: EK0526) was measured using Elisa Reader (BIO-TEK ELX800, USA)

Statistical Analysis

Results are given as mean ± standard deviation according to the data. Analyzes were done with GraphPad 7 statistical program (GraphPad Software, Inc., CA, USA). Mann-Whitney U test and One Way Anova test were used for statistical evaluation and $p<0.05$ was considered statistically significant.

Histological Analysis

Lung samples were fixed in 10% neutral formaldehyde solution for 3 days. The samples were then subjected to routine histological procedure and embedded in paraffin blocks. 5 μm sections were taken from the paraffin blocks with a microtome (Leica RM 2135). These sections were stained with hematoxylin and eosin. The preparations were examined with a conventional light microscope (Olympus BX51). The histologist, who did not know which group the animals belonged to, examined tissue damage with light microscopy as a blind observation of tissue edema formation, pulmonary structure, perivascular edema formation and inflammatory cell infiltration, and graded the results between 1 and 4 (11).

3. RESULTS

Histological scoring of acute lung injury of all experimental groups, MDA, CAT, GSH-Px, IL-1 α, TNF-α mean, standard deviation values , and statistical differences between the groups are shown in Table 2. A statistically significant difference was found between groups 2 and group 1, 3, 4, and 5 in terms of tissue edema formation, pulmonary structure, perivascular edema formation, and inflammatory cell infiltration between the groups ($p <0.05$). A statistically significant difference was found between groups 2 and group 1, 3, 4, and 5 in terms of tissue MDA levels, which is the end product of lipid peroxidation and an indicator of oxidative damage ($p <0.05$). There was a significant difference between groups 2 and groups 1, 4, and 5 in terms of the level of CAT enzyme, which enables hydrogen peroxide (H_2O_2) to be broken down into water and oxygen ($p <0.05$). A significant difference was found between group 2 and group 1, 3, 4, and 5 in terms of GSH-Px levels, which is an antioxidant parameter ($p <0.05$). There was no statistically significant difference between the groups in terms of IL-1α, TNF-α, levels ($p> 0.05$).
In the microscopic examination of the lungs of the rats belonging to the control group, the epithelium, connective, and muscle tissues, terminal bronchioles, and respiratory bronchioles were observed to be normal (Figure 1). In the microscopic examination of the lungs of rats belonging to the oleic acid group; Structural changes consistent with grade 3 characterized by the disappearance of bronchiole glands in the submucosa, hemorrhage, diffuse edema, dense neutrophil infiltration, hyalinization of the vascular wall, and diffuse necrosis were detected (Figure 2). Histological image belonging to DO group (Figure 3) Thickening of the interstitial area, less mononuclear cell infiltration compared to the oleic acid group, and minimal alveolar enlargement were observed. The histological image of the DOD group (Figure 4) was observed to have reduced mononuclear cell infiltration compared to the oleic acid group, terminal bronchioles were observed in a smooth appearance, and alveolar sacs were observed in normal appearance. The histological image of the OD group (Figure 5) was observed to have reduced mononuclear cell infiltration compared to the oleic acid group. Hemorrhagic areas are present but less observed than the oleic acid group.

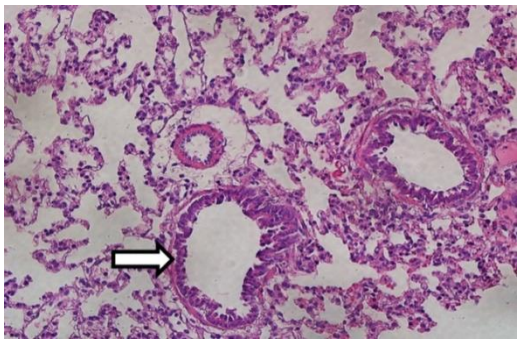

Figure 1. Normal lung histopathological appearance in the control group. The epithelium and muscle structure of the terminal bronchioles (arrow) are observed in normal thickness. (Hematoxylin-eosin X20) (Grade 1)

4.DISCUSSION

In the studies conducted, it has been determined that the acute lung injury model of oleic acid administered intravenously is a good model showing the clinical, pathological, and pathophysiological features of ARDS (12).

Ozdulger et al. (11) observed interstitial edema, intense inflammatory cell infiltration, and pulmonary deterioration in the histopathological examination of the lung tissue in the sepsis model caused by cecal ligation and puncture. It has been determined that N-Acetylcysteine, which has known antioxidant and anti-inflammatory properties, reduces interstitial edema, inflammatory cell infiltration, and pulmonary deterioration. In our study, acute respiratory distress syndrome was created with oleic acid. In our model created with oleic acid, lung damage was demonstrated by changes in MDA levels, GSH-Px, and CAT enzyme activities, supporting studies. Lung injury was supported by histopathological findings. In the microscopic examination of lung samples of rats belonging to the oleic acid group; Vascular congestion characterized by the disappearance of bronchiole glands in the submucosa, epithelial rashes in the alveolar spaces, interalveolar hemorrhage, diffuse edema, dense neutrophil infiltration, hyalinization of the vascular wall, and diffuse necrosis were observed.

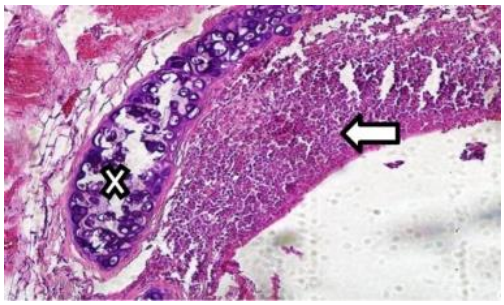

Figure 2. Hyaline cartilage degeneration (cross), mononuclear cell infiltration (arrow), connective tissue lost, cells degenerated (Hematoxylin-eosin x20) (Grade 3)

In the study of Koksel et al. (13), vascular congestion, neutrophil infiltration, and alveolar edema were observed in the histopathological examination of the lung tissue given oleic acid. In this study, it was reported that lung damage was reduced with the administration of Caffeic acid phenethyl ester (CAPE) and N-Acetylcysteine (NAC) with known antioxidant properties.

Kennedy et al. (14) observed pulmonary edema, diffuse neutrophil infiltration, increased capillary permeability, and decreased inflammation histopathologically in lung damage caused by oleic acid. When the lung tissue of rats given oleic acid was examined in the study conducted by Chen et al. (15), extensive edema and inflammatory cells were observed in the interalveolar area. In this study, it was determined in the study that propofol can reverse the changes due to oleic acid and reduce the degree of ALI before or after treatment. The positive effect of dexpanthenol in our study is similar to the results of this study.

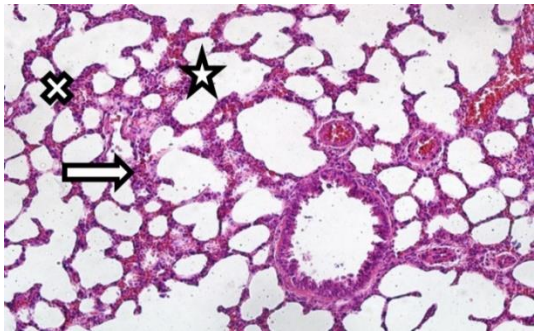

Figure 3. Thickening in the interstitial area (arrow), less mononuclear cell infiltration (cross) compared to the oleic acid group, Minimal alveolar enlargement (asterisks) (Hematoxylin-eosin x20) (Grade 2)

In various studies, different antioxidant and anti-inflammatory agents have been tried against experimental ARDS. In the studies of Zhu et al. (16), they found that ARDS induced with oleic acid can be effectively treated with the combination of exogenous surfactant treatment and inhaled nitric oxide (INO). Rebecca et al. (17) detected interstitial and interalveolar edema and alveolar hemorrhage when the acute lung injury caused by using oleic acid was examined histopathologically. In another study conducted by Lıu et al. (18), interstitial edema and pulmonary hemorrhage were observed when the rats with ARDS induced with oleic acid were examined histopathologically. It was observed that interstitial edema and pulmonary hemorrhage decreased in rats given superoxide dismutase (SOD) before the administration of oleic acid. In the microscopic examination of lung samples of rats belonging to the control group in our study; Terminal bronchioles and respiratory bronchioles consisting of epithelium, sub-epithelial connective tissue, and muscle cells just below were normal. Appearing to have a normal histological structure, no finding that could be evaluated as pathological was detected. Lung damage was detected histopathologically and biochemically in the oleic acid-treated but not treated group. The fact that dexpanthenol was given fewer neutrophils and the structure of terminal bronchioles was more uniform in the DO and DOD groups before the oleic acid administration and decreased mononuclear cell infiltration compared to the OA group support the idea that dexpanthenol has a possible protective effect. Studies of oleic acid in the literature support our study findings in terms of increasing total lung injury.
Licorice et al. (19) showed that intratracheal administration of hydrochloric acid to rabbits caused acute lung injury and increased plasma and BAL, MDA levels significantly. In our study, the fact that the tissue MDA levels were found in the group with the highest oleic acid and the lowest in the control group and a significant difference between the OA group and the K, DO, DOD, and OD groups support the thought that dexpanthenol has a possible healing and protective effect. Koksel et al. (13) found that CAPE reduced ARDS damage and increased MDA levels. In our study, a significant decrease in the MDA level in the dexpanthenol (DO) before oleic acid and after the oleic acid group in the dexpanthenol (OD) group compared to the OA group supports the study of Köksal et al.In our study, it was observed that dexpanthenol reduced the high MDA levels to the level of the control group, and this showed that dexpanthenol reduced oxidative damage.
The antioxidant effect of dexpanthenol has been determined in different experimental studies (20,22). GSH-Px levels have an important place in detecting this effect of dexpanthenol. Velmurugan et al. (21,29) observed an increase in GSH-Px enzyme activity after the administration of lycopene with known anti-oxidant properties in gastric carcinogenesis. A statistically significant difference was found between the OA group and the K, DO, DOD, and OD groups in terms of GSH-Px levels, which is one of the anti-oxidant parameters. Higher levels of GSH-Px in DO, DOD, OD groups were given dexpanthenol compared to OA, and control groups support our belief that dexpanthenol is protective as well as curative of acute lung injury. Leff et al. (23) found an increase in SOD and CAT activity and a decrease in GSH-Px activity in patients with sepsis who developed ARDS compared to those who did not. In our study, it was determined that the tissue GSH-Px enzyme activity showed values close to the control group in the OA group, and significantly increased in the OD, DOD, and DO groups given dexpanthenol compared to the OA group. In our study, it was determined that dexpanthenol increased antioxidant activity and prevented lipid peroxidation in acute lung injury. In our study, a significant difference was found between the OA group and the control and OD groups in terms of the level of CAT enzyme. Among the groups, the OA group had the lowest CAT enzyme activity, while the group with the highest enzyme activity was the control group. CAT values have been an important parameter for ARDS in experimental and clinical studies. Various publications support this (24). In the study of Salman et al., Who caused lung damage with oleic acid, it was found that oleic acid reduced CAT enzyme activity in lung tissue (26).

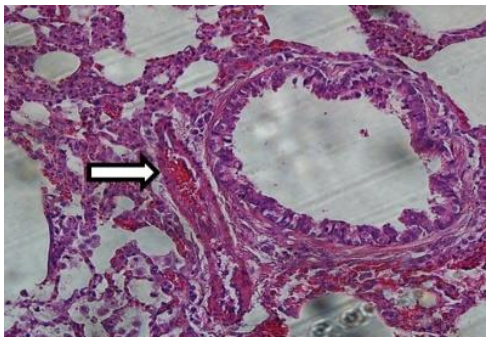

Figure 4. Mononuclear cell infiltration was observed to be less than the oleic acid group (arrow), terminal bronchioles were smooth, alveolar sacs were normal. (Hematoxylin-eosin X20) (Grade 2)

Bulmus et al. (25) reported that oleic acid decreased CAT enzyme activity in lung tissue in their study on lung injury induced by oleic acid in rats. Bulmuş et al. Observed that Alpha-Lipoic acid significantly increased the falling CAT level. In our study, the lowest CAT enzyme activity was found in the oleic acid group. The results obtained are parallel to our study.

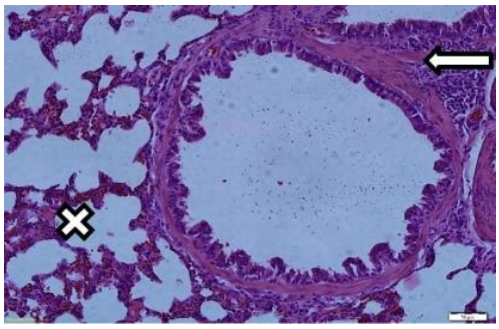

Figure 5. Mononuclear cell infiltration appears to be less than in the oleic acid group (arrow). Hemorrhagic areas are present but less observed (cross) compared to the oleic acid group. (Hematoxylin-eosin X20) (Grade 2)

Table 1. Histopathological scoring table

Grade 1:	Normal histopathology
Grade 2:	Mild neutrophil infiltration
Grade 3:	Moderate neutrophil infiltration, perivascular edema, alveolar edema, partial destruction of the pulmonary structure
Grade 4:	Dense neutrophil infiltration, abscess formation, complete deterioration of the pulmonary structure

There was no statistically significant difference between the groups in terms of IL-1α, TNF-α, levels. There are several possible reasons why IL-1α and TNF-α levels, which are pro-inflammatory cytokines that appear to play a role in lung pathologies such as ALI / ARDS and asthma, do not differ significantly between the groups (27). Our study is an animal study and these cytokines have been shown to play a role in the physiopathology of ALI / ARDS in humans. Another reason is that blood was taken from animals 4 hours after oleic acid administration and there was no time required for cytokines to rise. It has been reported that the time required for cytokines to rise reaches the highest level in the first 24 hours after oleic acid administration and remains high for about three weeks (13).
In the study conducted by Madtes et al., There is a study in which they showed that cytokine values are more effective in determining mortality on the 7th day compared to the 1st day (28). Our findings are early findings of ARDS whereas ARDS is a long process. He has publications that support our thinking (17). Another possible reason may be that the dose of oleic acid required to increase cytokines is not given.

The dose of oleic acid deemed necessary and the time required for blood collection after administration of oleic acid is controversial. Increasing the oleic acid dose and extending the time required to sacrifice the rats was considered as an alternative, but it was abandoned due to the necessity and difficulty of monitoring the animals in mechanical ventilation. We think that another possible reason is that these cytokines were worked manually with the ELISA method and the serum level was checked instead of the lung tissue.

The limitations of our study are as follows; The fact that the applications were carried out on experimental animals, the dose of oleic acid, how long after oleic acid was given, the damage occurred, and at what stage the damage occurred in clinical ARDS pathophysiology, the absence of a group that was given only dexpanthenol, and the fact that the ideal time to pass after dexpanthenol was not known is the limitations of our study.

Table 2. Histological scoring of acute lung injury of the experimental groups and biochemical analysis results of MDA, CAT, GSH-Px, IL-1 α, TNF-α mean, standard deviation values and statistical differences between groups

	Group 1 (C)	Group 2 (O)	Group 3 (DO)	Group 4 (DOD)	Group 5 (OD)
Histological1 Scores	1.000*±0	2.900±0.567	1.900*±0.567	1.900*±0.567	1.900*±0.567
MDA (nmol/g tissue)	10.99*±2.72	23.02±2.19	17.35*±3.53	17.20*±0.89	16.61*±0.51
CAT (mU/mL)	52.71*±9.46	29.63±7.00	31.18^{ns}±9.38	50.14*±8.94	52.67*±7.85
GSH-Px (mU/mL)	20.59*±2.34	16.32±0.89	21.12*±1.74	21.12*±3.29	20.70*±1.81
IL-1 **α** (pg/mL)	63.15^{ns}±4.74	67.21±7.45	62.94^{ns}±3.77	57.41^{ns}±9.60	62.66^{ns}±9.40
TNF-**α** (pg/mL)	53.17^{ns}±9.71	46.57±3.45	49.73^{ns}±5.79	45.57^{ns}±1.08	48.72^{ns}±3.51

* = If p <0.05 comparing result with O group, ns = Comparison with O group if p> 0.05

5. CONCLUSION

As a result, positive results were found with dexpanthenol administration in lung injury performed experimentally, and a significant improvement was found compared to the non-treated group. The finding of statistically significant differences in histopathological and biochemical parameters between the oleic acid applied group and the control group and the convergence of dexpanthenol application to the control group showed the effectiveness of dexpanthenol applied as therapeutic agent. Possible reasons for not detecting a significant difference in cytokine levels despite treatment were evaluated and it was concluded that these reasons were not directly related to the effectiveness of dexpanthenol. In line with all these results, it has been understood that dexpanthenol has protective and therapeutic effects on the ARDS model. Different treatment methods developed against lung damage, dexpanthenol is of great value as a therapeutic agent. Developing new approaches against lung damage, which is a major problem for human health with experimental methods, will be the basis for the development of new pharmacological preparations in the future. The emergence of different results, especially when applied as a precursor therapy and after ARDS, will provide support for the evaluation of the clinical use of long-term dexpanthenol use.

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