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Dexpanthenol and ascorbic acid ameliorate colistin-induced nephrotoxicity in rats

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Abstract. – OBJECTIVE: Colistin is a potent antibiotic which is mainly preferred in the treatment of multidrug-resistant (MDR) gram-negative bacilli. However, due to the increased risk of acute kidney injury following its use, the clinical application is limited. This nephrotoxicity is known to be induced by oxidative stress and related inflammation. In this study on rats, potent antioxidants Dexpanthenol (DEX) and Ascorbic acid (Vit C) have been administered in combination with Colistin to find out whether they would weaken Colistin's nephrotoxic effects.

MATERIALS AND METHODS: Inflammation biomarkers were studied with enzyme-linked immunosorbent assay (ELISA) kits, and oxidative stress biomarkers were studied with different photometric methods in blood and tissue samples taken after treatment with DEX and Vit C in rats with colistin nephrotoxicity. In addition, inflammation and necrosis in the kidney tissues were examined pathologically.

RESULTS: It has been observed in the serum and tissue samples that DEX and Vit C decrease oxidative stress and inflammation biomarkers, therefore acting as nephroprotective agents.

CONCLUSIONS: These compounds have been found to ameliorate the nephrotoxic effects of Colistin, which were demonstrated in the rats treated with Colistin, as well as the combinations.

Key Words:
Colistin-induced nephrotoxicity, Dexpanthenol, Ascorbic acid, Oxidative stress, Inflammation.

Introduction

Nosocomial infections and outbreaks such as those caused by multidrug-resistant (MDR) gram-negative bacilli including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, continue becoming globally more prevalent[1,2]. Serious difficulties emerge in the treatment of these infections due to the lack of capability in the development of effective novel antibiotics while the resistance spreads[2]. One of the most commonly used antibiotics in the treatment of these infections is Colistin (also known as polymyxin E)[2,3]. Colistin is a bactericidal polypeptide which is found effective against many gram-negative microorganisms, disrupts the membrane stabilization, hence leading to the death of bacteria[3,4]. The most important side effect of Colistin which limits its clinical use is nephrotoxicity[3,5,6]. It has been reported that among the patients treated with Colistin, the occurrence of acute kidney failure reaches up to

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50-60%[6]. It has been proved that this nephrotoxicity is caused due to the oxidative damage and inflammation induced by Colistin[7,8]. Therefore many antioxidants have been investigated *in vivo* for their effect on nephrotoxicity caused by Colistin[4,9-14]. One of the antioxidants that has been tested for this purpose is Ascorbic acid (Vit C). It has been suggested that Ascorbic acid prevents Colistin-induced nephrotoxicity due to its antioxidant properties[9]. In a prospective human study that included a Colistin treatment group, Ascorbic acid was shown to be nephroprotective[15].

Dexpanthenol (DEX), which is an alcohol derivative of pantothenic acid (B_5), is an antioxidant similar to Ascorbic acid which inhibits free radical formation[16]. DEX is being used clinically for various indications, and *in vivo* studies have demonstrated its ability to decrease amikacin nephrotoxicity and cisplatin hepatotoxicity[17,18].

In this study, it has been aimed to observe the nephroprotective properties of DEX and Vit C against Colistin nephrotoxicity in an experimental rat model.

Materials and Methods

In our study, approval was obtained from Bezmialem Vakif University Experimental Animals Local Ethics Committee (BVU-HAYDEK) with an ethical report numbered 2016/316. In the experiments, 48 Sprague Dawley male rats, 3 months old, 250-300 g in weight, provided by Bezmialem Vakif University Experimental Animals Laboratory were used. Rats were housed in normal cages at room temperature of 24 ± 3ºC. The 12-hour light/dark cycle was respected. Rats were randomly selected and divided into 6 groups, with 8 rats in each group. Group 1 (n = 8) was determined as the "Control Group" and Saline was administered intraperitoneally (i.p.) for 14 days. Group 2 was designated as the (n = 8) "Sham Group/Colistin (COL) Group" and injected 15 mg/kg Colistin intraperitoneally every other day for a total of 14 days (15 mg/kg * 2/day). Group 3 (n = 8) was designated as "Vit C Group" and injected with Vitamin C for 14 days at a dose of 100 mg/kg * 2/day (i.p.). Group 4 (n = 8) was determined as "DEX Group" and Dexpanthenol was injected intraperitoneally at a dose of 250 mg/kg * 2/day for 14 days. Group 5 (n = 8) was designated as "Colistin + Vit C Group" and injected with 15 mg/kg * 2/day Colistin (i.p.) and 100 mg/kg * 2/day Vitamin C (i.p.) for 14 days. Group 6 (n = 8) was designated as "Colistin + DEX Group" and injected intraperitoneally with 15 mg/kg * 2/day Colistin and 250 mg/kg * 2/day Dexpanthenol for 14 days. On the 15th day, the animals were sacrificed, and the intracardially collected blood was separated into their serums. One of the kidneys was taken to buffered formaldehyde for pathological examination. The other kidney was taken for biochemical analysis, homogenized, and protein determined by the Bradford method[19]. Total antioxidant level (TAS)[20], total oxidant level (TOS)[21], and markers of the oxidative stress profile in serum and tissue were measured photometrically using an automated method developed by Erel, Erel's photometric methods were also utilized in the measurement of total thiol (TT) and native thiol (NT) levels[22]. Oxidative stress index (OSI: TOS / TAS) and disulfide levels (DIS: (TT-NT) / 2) were calculated with mathematical formulas. Serum and tissue Interleukin 1β (IL-1β), Interleukin 6 (IL-6), Tumor Necrosis Factor-α (TNF-α), and high sensitivity C-Reactive Protein (hs-CRP) levels were measured spectrophotometrically with commercially purchased enzyme-bound immunosorbent test, enzyme-bound immunoassay kit (ELISA) kits. Serum urea and creatinine levels were measured in Abbott Architect c16000 autoanalyzer by enzymatic methods. A complete urinalysis was performed with a strip in the collected urine. Data has been analyzed with the package program IBM SPSS Stat. 22.0 (IBM, Armonk, NY, USA). The statistical analysis among groups has been executed by Mann Whitney-*U* test. Results are given as Mean ± Standard Deviation (Mean ± SD). $p<0.05$ was considered statistically significant.

Results

Pathological Scoring

The renal tissues of the Control, DEX, and Vit C Groups appeared normal under the light microscope. Similarly, the histopathological appearances of DEX and Vit C Groups were close to normal. Desquamation, inflammation, and necrosis were observed in the proximal tubules in Colistin treated rats (Figure 1). In addition, in all Colistin-given groups, almost all rats had sporadically significant mononuclear inflammatory cell infiltration. No sclerosis was observed in the glomeruli. Focal granulovacuolar changes and rare desquamation were present in the proximal

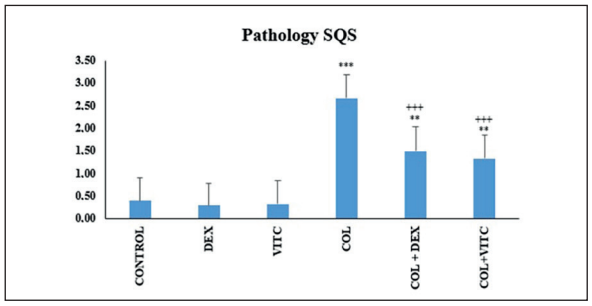

Figure 1. Pathological semi-quantitative scoring statistically increased in Colistin groups (COL, COL + DEX and COL + VITC) compared to the control group (healthy). In addition, decreases in all treatment groups compared to the Colistin group are statistically significant. * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$ & + = $p<0.05$; ++ = $p<0.01$; +++ = $p<0.001$.

tubules of the treatment groups. Inflammation, necrosis, and desquamations in tissues decreased statistically significantly with the treatments given.

Oxidative Stress

Serum and kidney tissue TAS values of the group given Colistin alone (0.62 mmol Trolox Equiv/L and 0.21 mmol Trolox Equiv/L mg protein) compared to the control group (1.00, 0.40 mmol Trolox Equiv/L) were found significantly lower ($p<0.05$). However, TAS values of the groups' given DEX or Vit C together with Colistin (COL+DEX and COL+VIT C groups) were significantly higher ($p<0.05$) than the Colistin Group (Figure 2).

Both serum and kidney tissue TOS values (15.87 µmol H_2O_2 equiv./L and 6.23 µmol H_2O_2 equiv./L mg protein, respectively) and OSI values (25.57 AU and 31.05 AU mg protein, respectively) of the Colistin group were found significantly higher ($p<0.05$) compared to the control group's TOS (9.06 µmol H_2O_2 equiv./L and 3.94 µmol H_2O_2 equiv./L mg protein) and OSI (9.77 AU and 10.06 AU mg protein) values. However, TOS and OSI values of Colistin + Dexpanthenol (COL+-DEX) and Colistin + Ascorbic Acid (COL+VIT C) groups were significantly lower ($p<0.05$) compared to the Colistin group (Figure 3).

Serum TT and NT values were significantly lower in the Colistin Group (0.39 and 0.16 mmol/L, respectively) compared to the Control Group (0.51 and 0.37 mmol/L, respectively). The values of the groups' given Dexpanthenol (COL+DEX) or Vitamin C (COL+VIT C) together with Colistin (0.50, 0.33 mmol/L, and

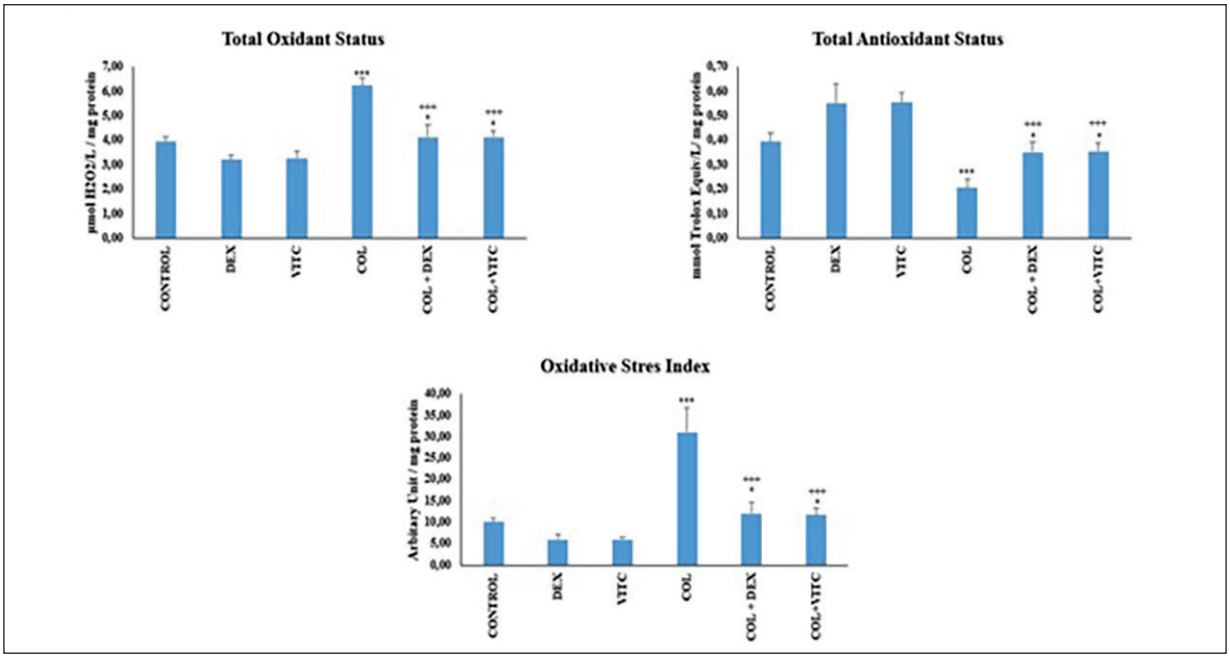

Figure 2. Tissue Total Oxidant Status (TOS) and Oxidative Stress Index (OSI) increased significantly in Colistin groups (COL, COL + DEX and COL + Vit C) compared to the Control Group (healthy). In addition, decreases in all treatment groups compared to the Colistin Group are statistically significant. Total Antioxidant Status (TAS) decreased statistically in the Colistin Group compared to the Control Group. Also, in the Colistin treatment groups, the Total Antioxidant Status (TAS) increased statistically compared to the colistin group. * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$ & + = $p<0.05$; ++ = $p<0.01$; +++ = $p<0.001$.

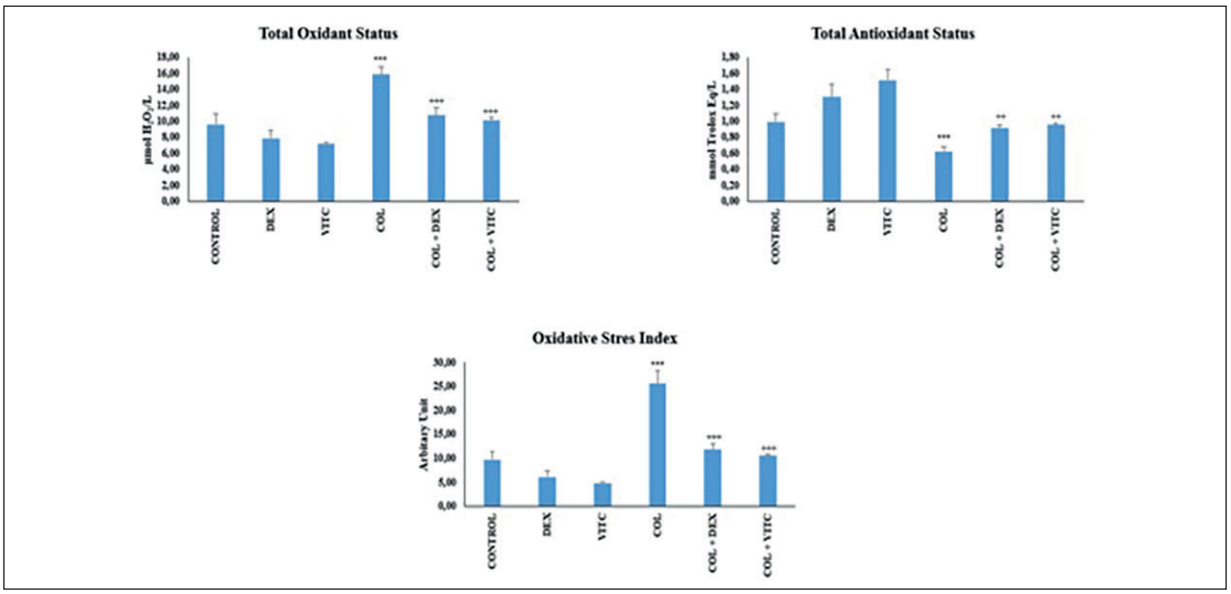

Figure 3. Serum Total Oxidant Status (TOS) and Oxidative Stress Index (OSI) increased significantly in colistin groups (COL, COL + DEX and COL + VITC) compared to the control group (healthy). In addition, decreases in all treatment groups compared to the colistin group are statistically significant. Total Antioxidant Status (TAS) decreased statistically in the Colistin group compared to the control group. In the Colistin treatment groups, the Total Antioxidant Status (TAS) increased statistically compared to the Colistin Group. * = p<0.05; ** = p<0.01; *** = p<0.001 & + = p<0.05; ++ = p<0.01; +++ = p<0.001.

0.52, 0.36 mmol/L, respectively) were significantly higher than the group given Colistin alone (p<0.05).

Serum DIS levels of the Colistin group (0.12 mmol/L) were significantly higher than the control group (0.008 mmol/L). However, the values of the Colistin + Dexpanthenol (COL+DEX) and Colistin + Ascorbic Acid (COL+VIT C) groups were found to be significantly lower than the Colistin Group (Figure 4).

Inflammation

Serum (IL-6: 154.19 ng/L, IL-1β: 344.50 pg/L, TNF-α: 193.41 ng/L, hsCRP: 505.28 µg/mL) and kidney tissue (IL-6: 75.62 ng/L mg protein, IL-1β: 102,16 pg/L mg protein and TNF-α: 142.57 ng/L mg protein, respectively) inflammatory markers of the Colistin group were significantly higher (p<0.05) than the control group (Serum; IL-6: 106.35 ng/L, IL-1β: 184.65 pg/L, TNF-α: 149.33 ng/L ve hsCRP: 317.22 µg/mL and kidney tissue; IL-6: 55.19 ng/L mg protein, IL-1β: 48,85 pg/L mg protein, TNF-α: 111.92 ng/L mg protein). The values of the Colistin + Dexpanthenol (COL+-DEX) Group (Serum; IL-6: 114.64 ng/L, IL-1β: 293.53 pg/L, TNF-α: 165.32 ng/L, hsCRP: 394.00 µg/ml and kidney tissue; IL-6: 63.48 ng/L mg protein, IL-1β: 68.60 pg/L mg protein, TNF-α: 115.47 ng/L mg protein) and Colistin + Ascorbic Acid (COL+VIT C) groups (Serum; IL-6: 113.61 ng/L, IL-1β: 293.29 pg/L, TNF-α: 164.62 ng/L, hsCRP: 393.00 µg/ml and kidney tissue; IL-6: 63.51 ng/L mg protein, IL-1β: 65.18 pg/L mg protein, TNF-α: 115.39 ng/L mg protein) were significantly (p<0.001) lower than the Control Group (Figures 5 and 6).

Serum urea and creatinine values (50.67 mg/dL, 1.56 mg/dL, respectively) of the group given Colistin alone (0.35 mg/dL, 0.80 mg/dL, respectively) compared to the Control Group was found significantly higher (p<0.05). Urine and creatinine values (Colistin + Dexpanthenol group: 39.67 mg/dL, 0.95 mg/dL and Colistin + Vit C group: 39.17 mg/dL, 0.95 mg/dL, respectively) of the groups given Dexpanthenol or Vitamin C together with Colistin (COL+DEX and COL+VIT C groups) were found to be significantly (p<0.05) lower (Figure 7).

Discussion

Colistin is an important antibiotic used in the treatment of gram-negative bacilli. However, its nephrotoxicity limits its optimum application. Oxidative stress and the inflammation it leads to

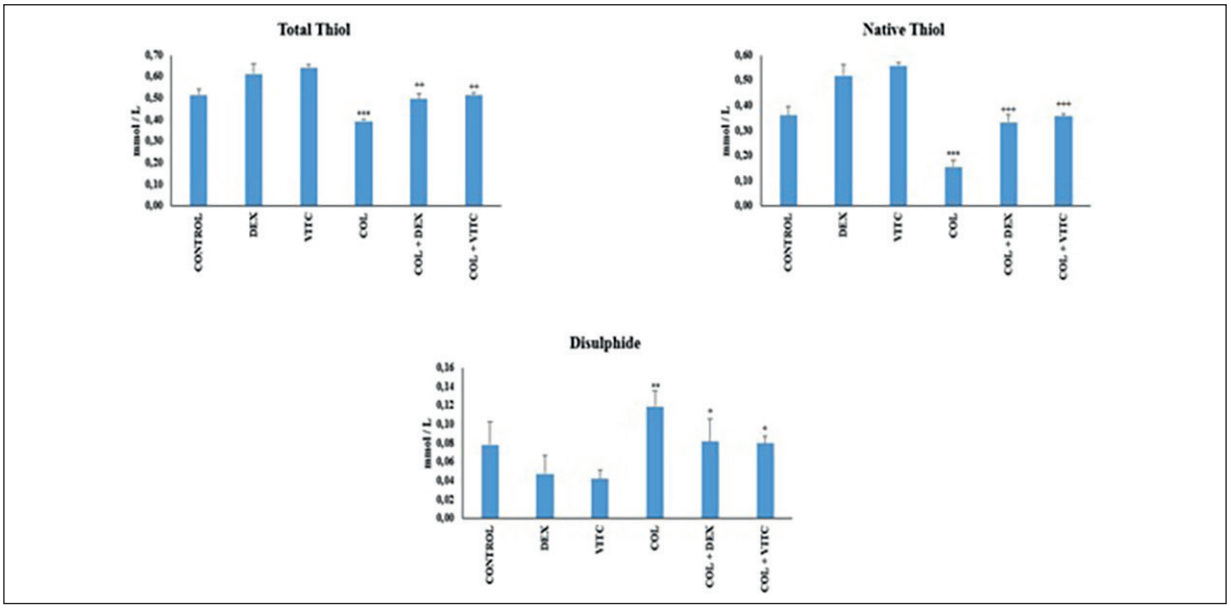

Figure 4. Serum Disulfide level increased statistically significantly in Colistin groups (COL, COL + DEX and COL + VIT C) compared to the Control Group (healthy). Additionally, decreases in all treatment groups compared to the Colistin Group are statistically significant. Total Thiol and Native Thiol levels decreased statistically in the Colistin Group compared to the Control Group. Furthermore, in the Colistin treatment groups, the Total and Native Thiol levels statistically increased compared to the Colistin Group. * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$ & + = $p<0.05$; ++ = $p<0.01$; +++ = $p<0.001$.

play a major role in drug-induced organ damage as in many other diseases[4]. As mentioned above, oxidative stress and inflammation have a notable part in the pathogenesis of Colistin induced nephrotoxicity. In this study, nephrotoxicity has been observed secondary to oxidative stress and

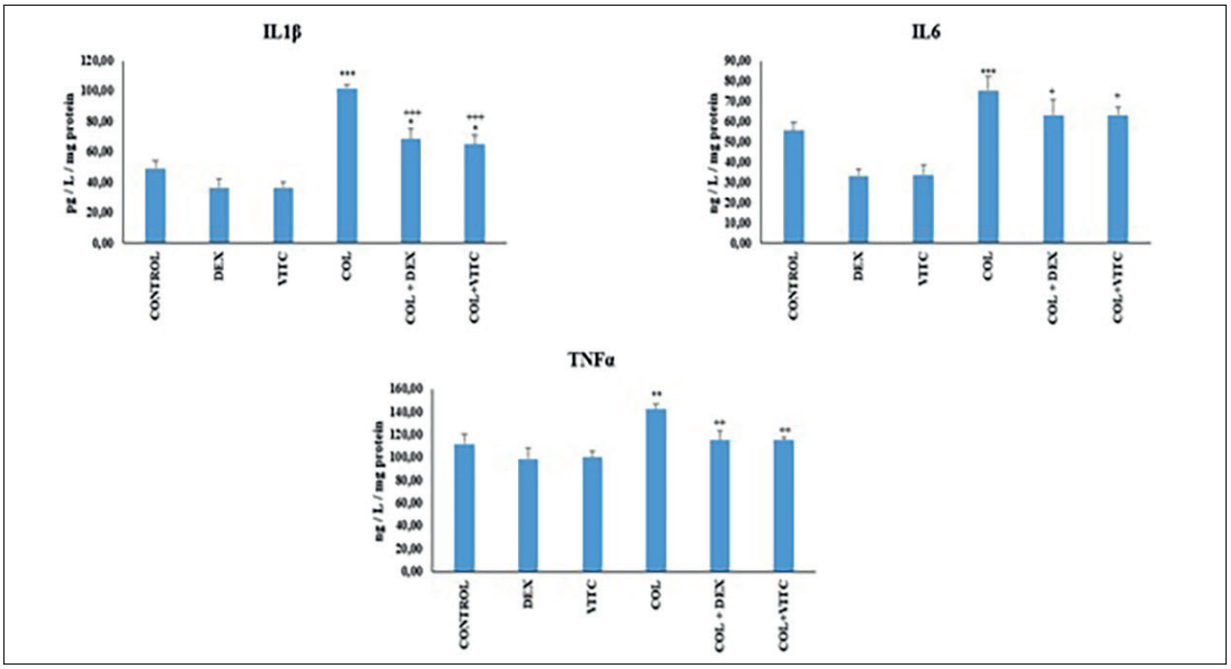

Figure 5. Tissue IL1-β, IL-6 and TNF-α values increased statistically significantly in Colistin groups (COL, COL + DEX and COL + VIT C) compared to the Control Group (healthy). Also, decreases in all treatment groups compared to the Colistin Group are statistically significant. * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$ & + = $p<0.05$; ++ = $p<0.01$; +++ = $p<0.001$.

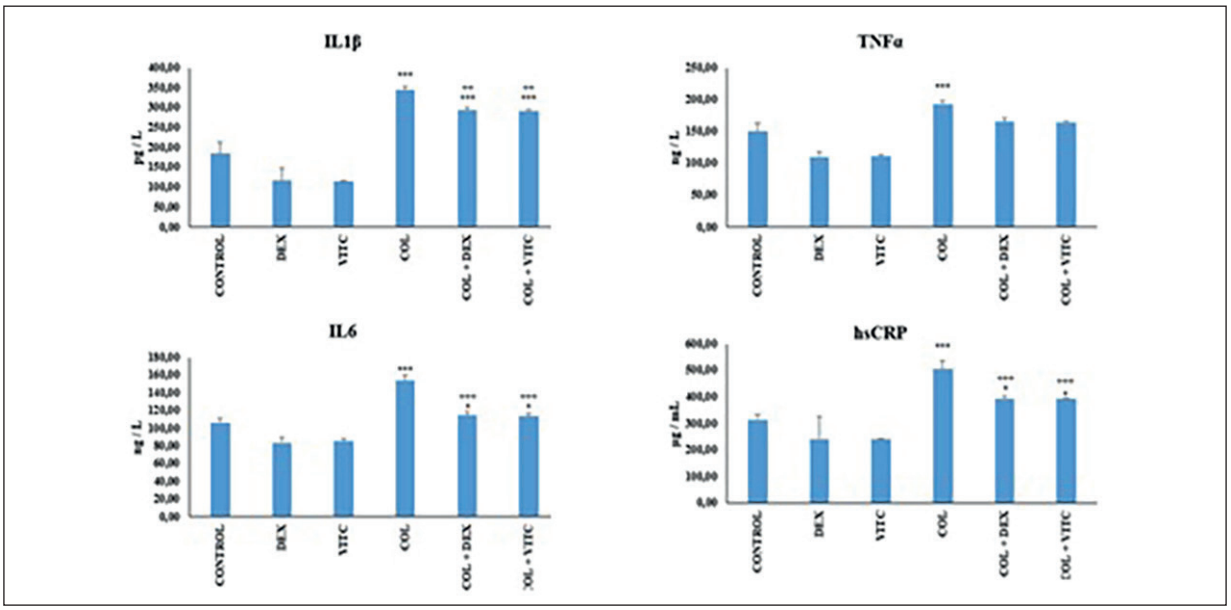

Figure 6. Serum IL1-β, IL-6, TNF-α, and hsCRP levels increased statistically significantly in Colistin groups (COL, COL + DEX and COL + VIT C) compared to the Control Group (healthy). Likewise, decreases in all treatment groups compared to the Colistin Group are statistically significant. * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$ & + = $p<0.05$; ++ = $p<0.01$; +++ = $p<0.001$

inflammation in rats treated with Colistin, which is in line with other studies. However, when DEX and Vit C were administered along with Colistin, a significant decrease was observed in oxidative stress and inflammation markers, while no nephrotoxicity occurred. Compared with the control group, no significant change was found in urea, creatinine, oxidative stress, and inflammatory markers in the serum and tissues of treated rats. DEX and Vit C have been found similar in their healing properties on Colistin-induced nephrotoxicity; however, the superiority of one over the other could not be identified.

In rats which curcumin, an antioxidant, is administered, catalase and reduced glutathione levels have been found increased in renal and brain tissues, while malondialdehyde (MDA) has been found decreased[4]. In another experimental study, in rats treated solely with Colistin, the activity of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) enzymes were decreased significantly. Still, when Colistin was applied in combination with vitamin E and C, a significant increase was observed[10].

When amikacin has been tried in a combined therapy with DEX instead of single amikacin treatment in rats, a significant decrease has been observed in OSI and TOS while TAS, CAT, PON1, and ARES activities have significantly increased[17].

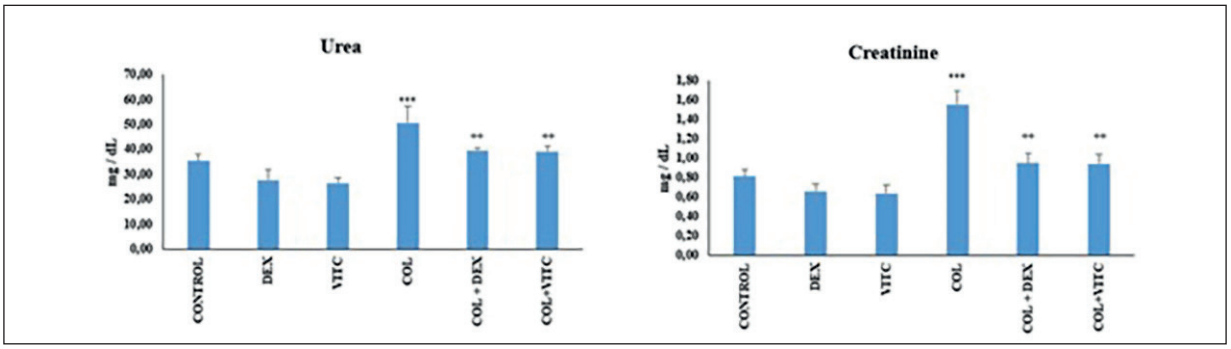

Figure 7. Serum Urea and Creatinine levels increased statistically significantly in Colistin groups (COL, COL + DEX and COL + VITC) compared to the Control Group (healthy). In addition, decreases in all treatment groups compared to the Colistin Group are statistically significant. * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$ & + = $p<0.05$; ++ = $p<0.01$; +++ = $p<0.001$.

In study investigating the effects of baicalein on Colistin-induced oxidative stress, the use of baicalein has been shown to decrease the levels of MDA and nitric oxide (NO) and the activity of inducible nitric oxide synthase (iNOS) enzyme while increasing SOD, CAT, and GSH levels[11]. SOD levels have been spotted higher in renal tissues of rats when Colistin is administered alone, but they appeared to be normal in the case Colistin is used with N-Acetyl Cysteine[12]. Due to the use of colistin, an increase in mitochondrial superoxide (MitoSOX) level has been identified. However, when the combination of colistin and methionine was used, the MitoSOX level appeared to drop by half[23].

All these studies demonstrate that colistin increases oxidative stress in tissues and serum, with which our research findings align.

Renal and cerebral TNF-α and IL-6 levels in the antioxidant curcumin combination group have been observed significantly lower than the single Colistin treatment group[4]. The use of baicalein has been found to decrease renal TNF-α and IL-1β levels compared to the Colistin group[11]. In accordance with these data, our experiment found that the serum and tissue IL-1β, IL-6, and TNF-α levels have been higher in the single Colistin treatment group. The use of DEX or Vit C has been observed to lower these values to the reference range.

Research on the nephroprotective features of DEX in rats has shown that DEX managed to normalize amikacin related increased creatinine and BUN levels[17]. In our study, Colistin and DEX combination group has been found to significantly lower the levels of urea and creatinine in comparison with the Colistin treatment group. Yousef et al[9] present that rats have higher creatinine levels when treated with Colistin, while rats treated with Colistin and Vit C (200 mg/kg) have normal levels of creatinine. Our findings comply with previous research in which Colistin and high dose Vit C (200 mg/kg) combination leads to normal levels of urea and creatinine in rats in the case of Colistin-induced nephrotoxicity. A recent *in vivo* study reports that treatment of Colistin leads to lower creatinine and urea levels if combined with curcumin, which is a potent antioxidant[24]. In a similar manner, baicalein has been found to decrease Colistin related high urea and creatinine levels due to colistin[11]. The same effect has been observed in similar studies that analyzed melatonin, luteolin, and N-Acetyl Cysteine[13,14,25,26].

Similar results have been obtained when colistin and DEX combination treatment had been compared with Colistin and Vit C combination regarding all investigated serum and tissue parameters. A statistically significant difference has not been detected. This experimental model has indicated that DEX bears nephroprotective characteristics as much as Vit C.

Limitations

One of the most important limitations is that the effects of DEX or Vit C administration in combination with Colistin on the pharmacokinetics and pharmacodynamics of Colistin have not been investigated. Another limitation is that different doses of neither DEX nor Vit C have been tested due to the high costs.

Effects on Human Studies

The main obstacle in the optimal use of Colistin is its nephrotoxicity. This experimental study in rats has shown that DEX and Vit C are nephroprotective in Colistin treatment. It is advised that the nephroprotective effects of Dexpanthenol, which has several clinical indications, and Ascorbic acid should be investigated in humans going through Colistin treatment.

Conclusions

This study demonstrated that Colistin leads to nephrotoxicity via increased oxidative stress, inflammation, and tissue damage. However, when Colistin is administered with potent antioxidants, such as DEX and Vit C, it has been observed that oxidative stress, inflammation, and tissue damage were prevented.

When the nephroprotective characteristics of DEX and Vit C, which were found to lower the damaging effects of colistin, were compared, no significant difference was observed. This paper is the first study stating that DEX and Vit C are protective against Colistin-induced nephrotoxicity.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Source of Funding

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