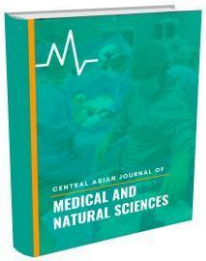

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Article

The Protective Effects of Administration of Antioxidant and Steroid on Renal Tissue Injury After Ischemia-Reperfusion in Rats

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Abstract: Renal ischemia-reperfusion represents the major cause of acute kidney injury, causing oxidative stress and inflammation in renal tissue. Assessment the relative and combined protective effects of these agents on renal histopathological changes following ischemia-reperfusion injury in male rats. A total of 30 healthy adult male rats were purchased, acclimated, and divided randomly and equally to six groups as following: sham (neither treated nor surgically operated), ischemia-reperfusion (subjected to initiation of left renal ischemia by reperfusion for 1 hour), vitamin C treatment (administered 150mg/kg ascorbic acid intravenously immediately at beginning of reperfusion), vitamin E treatment (received 100mg/kg vitamin E intramuscularly 15 minutes before reperfusion), hydrocortisone treatment (received 50mg/kg hydrocortisone intravenously immediately at beginning of reperfusion), and combination therapy (underwent ischemia-reperfusion and received vitamins C and E as well as hydrocortisone). After scarification, renal tissues of study rats were collected, processed histopathologically, and examined under light microscopic. Histological examination of kidney sections showed that renal architecture of Sham group was normal and no degeneration and necrosis were observed with histopathological scores recorded at zero. In contrast, renal injury was seen in ischemia-reperfusion group; in which, severe vacuolar degeneration and necrosis proximal and distal tubules, swollen in tubular epithelial cells, cytoplasmic vacuolization, loss of brush border, sloughing of epithelial cells from basement membrane, tubular necrosis, atrophic glomeruli, and marked vascular congestion and hemorrhage in interstitium. For vitamin C group, there was a reduction in severity of tubular injury with mild degenerative changes in proximal tubular epithelium and renal structure. Concerning the vitamin E and hydrocortisone, renal sections were moderately improved and tubular degeneration was lessened. Regarding vitamin E group, mild to moderate degeneration; while, in hydrocortisone group, moderate vacuolar degeneration but less frequent necrosis was observed. Among all treated groups, combination treatment group showed the higher scores of tubular degenerations, tubular necrosis, tubule-interstitial inflammation, and total histological score suggesting the highest protective power. Administration of a combination of vitamins C and E with hydrocortisone were synergistically protect ischemia-reperfusion injured kidney and almost completely prevents destruction of tubular structure and inflammation in reperfused kidneys. However, furthermore studies are of great importance to support our work.

Keywords: Ascorbic Acid, Histopathology, Hydrocortisone, Iraq, Tocopherol, Vitamins

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1. Introduction

Renal ischemia-reperfusion injury is a primary cause of acute kidney injury and remains a crucial clinical issue in renal transplantation, cardiothoracic surgeries, trauma, as well as shock states [1]. The ischemic phase decreases ATP, hence cellular hypoxia, while reperfusion paradoxically accentuates tissue damage through intense production of reactive oxygen species, endothelial dysfunction, mitochondrial injury, furthermore activation of inflammatory cascades [2]. The proximal tubules are highly sensitive because their metabolic needs are high; in contrast, they have only a limited antioxidant buffer [3]. Inflammation and oxidative stress are widely acknowledged as important mechanisms underlying renal ischemia-reperfusion injury. Thus, experimental research has focused on therapeutic interventions that target these pathways. Ascorbic acid, or vitamin C, functions as a hydrophilic antioxidant that improves microvascular perfusion, regenerates vitamin E, and neutralizes ROS [4], [5]. As a lipid-soluble antioxidant, vitamin E (α-tocopherol) protects cell and mitochondrial membranes from lipid peroxidation, preserving structural integrity under oxidative stress [6]. By suppressing pro-inflammatory cytokines, leukocyte recruitment, and vascular permeability, significant mediators of tissue damage linked to ischemia-reperfusion-hydrocortisone, a glucocorticoid, has potent anti-inflammatory effects [7] [8].

Recent experimental work suggests that combination therapy involving antioxidants and anti-inflammatory agents may yield synergistic protective effects, as each agent targets distinct but interrelated pathways of injury [9], [10], [11]. However, comparative studies evaluating vitamin C, vitamin E, and hydrocortisone individually and in combination in renal ischemia-reperfusion models remain limited. Therefore, the present study aimed to assess the relative and combined protective effects of these agents on renal histopathological changes following ischemia-reperfusion injury in male rats.

2. Materials and Methods

Experimental Animals

Thirty healthy adult male rats were used in this study. The animals were maintained under standard conditions of temperature, 12-hour day-night cycles, and had free access to food and water. All experiments were carried out in accordance with ethical guidelines for working with laboratory animals.

Experimental Design

The rats were randomly divided into six groups, each group containing five animals:

- Group 1 (sham): Rats neither treated nor surgically operated.
- Group 2 (ischemia-reperfusion): Rats were subjected to the initiation of left renal ischemia by reperfusion for 1 hour.
- Group 3 (vitamin C treatment): Rats were administered 150mg/kg ascorbic acid intravenously immediately at the beginning of reperfusion.
- Group 4 (vitamin E treatment): Rats received 100mg/kg vitamin E intramuscularly 15 minutes before reperfusion.
- Group 5 (Hydrocortisone treatment): Rats received 50mg/kg hydrocortisone intravenously immediately at the beginning of reperfusion.
- Group 6 (Combination therapy): Rats underwent ischemia-reperfusion and received vitamin C, 150mg/kg IV, vitamin E, 100mg/kg IM, and hydrocortisone, 50mg/kg IV, administered in the same way as in the respective treatment groups.

Induction of Renal Ischemia-Reperfusion

Anesthesia was induced by injecting ketamine at a dose rate of 90 mg/kg and xylazine at 10 mg/kg intramuscularly. Each rat was placed in dorsal recumbency, and through a midline abdominal incision, the intestines were gently retracted to expose the abdominal aorta. Renal ischemia was then induced by placing a microvascular clamp on

the proximal abdominal aorta above the renal arteries. During ischemia, the abdomen was temporarily closed to prevent fluid and heat loss. The clamp was removed to allow reperfusion after 45 minutes. One hour following reperfusion, the animals were euthanized by chloroform absolute (BDH England). The left kidney was immediately harvested for histopathological evaluation.

Histological Processing

The excised kidneys were fixed in 10% neutral buffered formalin, dehydrated, embedded in paraffin, and sectioned at 5μm thickness. Slides were prepared and stained with H & E. All samples were examined by a blinded histopathologist using light microscopy [12].

The renal tissue injury was assessed semi-quantitatively according to the severity of:

- Tubular degeneration (TD).
- Tubular necrosis (TN).
- Tubulointerstitial nephritis (TIN).

Table 1. Tubular Degeneration (TD) and Tubular Necrosis (TN).

Score	Description
0	No detectable tubular degeneration or necrosis
1 (Mild)	Small and limited focal areas of degeneration/necrosis located just beneath the capsule (0–10% of tissue involvement)
2 (Moderate)	Multiple focal areas of degeneration/necrosis extending along tubular segments (10–25% involvement)
3 (Severe)	Diffuse and pronounced degeneration/necrosis affecting large areas of the renal tubules (25–50% involvement)
4 (Very severe)	Extensive degeneration/necrosis involving more than 50% of examined tubules

Table 2. Tubulointerstitial Nephritis (TIN).

Score	Description
0	No inflammatory cell infiltration.
1 (Mild)	Few inflammatory cells localized around blood vessels (0–5% involvement)
2 (Moderate)	Inflammatory infiltration extending into cortical interstitial areas with multiple foci (5–10% involvement)
3 (Severe)	Diffuse and significant inflammatory cell infiltration in interstitial tissue (15–25% involvement)
4 (Very Severe)	Widespread inflammation involving more than 50% of the renal cortex

Table 3. Interpretation of THS values.

Value Range	Interpretation
0–2	Normal renal histology
2–5	Mild renal injury
5–8	Moderate renal injury
> 8	Severe renal injury

- Tubular degeneration was defined as cytoplasmic vacuolization and granular degeneration in proximal tubule epithelial cells.
- Tubular necrosis was identified by nuclear loss, highly eosinophilic cytoplasm, and cell detachment into the tubular lumen.
- Tubulointerstitial nephritis was defined as leukocyte infiltration in interstitial and perivascular areas.

Each of the treatment groups' histopathological findings was compared to those of the untreated ischemia-reperfusion group in order to determine the relative degree of renal protection.

Statistical Analysis

Data from histopathological scoring are presented as median and interquartile range (IQR). Because the data were non-parametric, group comparisons were done using the Kruskal–Wallis test, followed by a post-hoc Dunn's multiple comparisons test to assess pairwise differences between groups. For statistical analysis, GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA) was used to indicate significant differences at $p<0.05$ [13].

3. Results

Histological examination of kidney sections in the sham group showed that renal architecture was normal, glomeruli and tubular epithelial cells remained intact, and no degeneration and necrosis were observed, see Figure 1. In this group, all histopathological scores were recorded as zero.

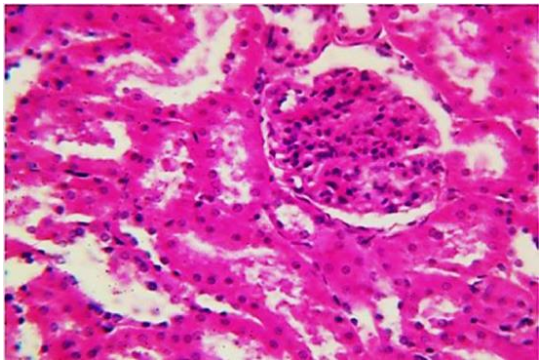

Figure 1. Histopathological section of the kidney in 1st group (sham group) showed: Normal architecture of the kidney (sham group) (H &E, ×400).

In contrast, there was widespread renal injury in the ischemia-reperfusion group. Both the proximal and distal tubules showed severe vacuolar degeneration and necrosis. Tubular epithelial cells were swollen, with striking cytoplasmic vacuolization. Brush border loss, with sloughing of epithelial cells from the basement membrane, was noted. Tubular necrosis included pyknotic or absent nuclei. Glomeruli were atrophic, showing widened urinary spaces. Marked vascular congestion and hemorrhage were also present in the interstitium, see Figure 2.

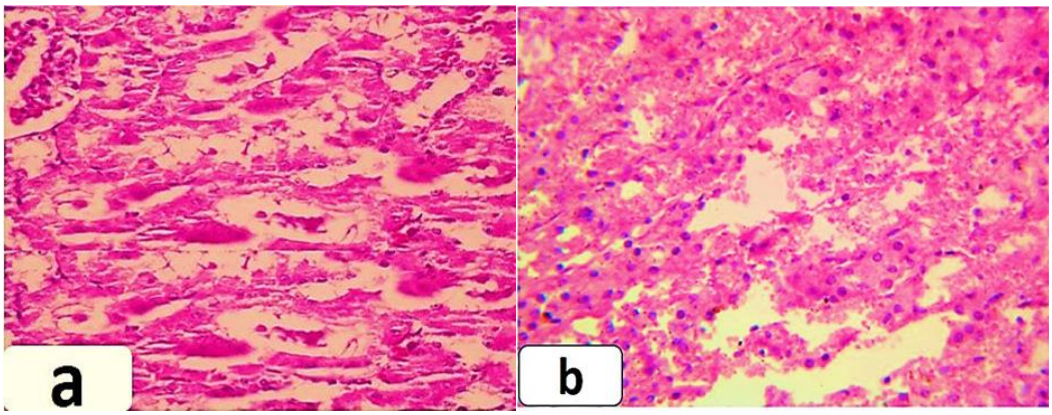

Figure 2. Histopathological section of kidney in the 2nd group (ischemia-reperfusion) showed: (a) Severe tubular epithelial degeneration and necrosis; (b) tubular degeneration and necrosis (H &E, ×400).

Renal tissue from the animals in the vitamin C group clearly showed a reduction in the severity of the tubular injury. Only mild degenerative changes could be seen in the proximal tubular epithelium, and the renal structure was generally preserved, see Figure 2.

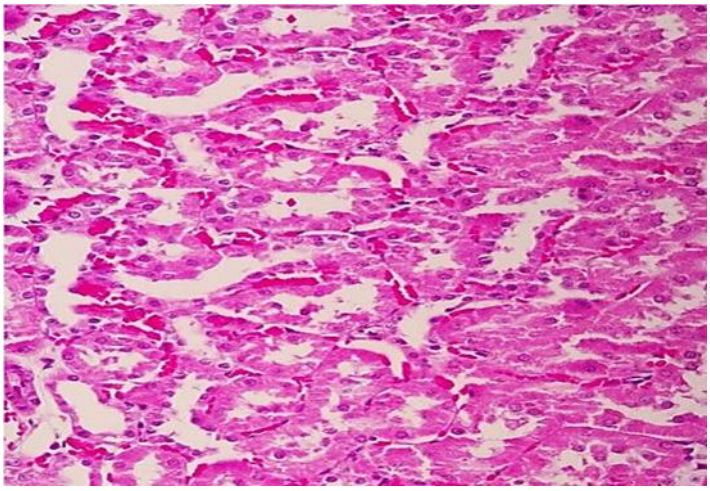

Figure 3. Histopathological section of kidney in the 3rd group (vitamin C treatment) showed: Mild tubular epithelial degeneration with partially preserved tubular structures; (H &E, × 400).

In the groups treated with vitamin E and hydrocortisone, renal sections showed moderate improvements in histology when compared with the ischemia-reperfusion group. Tubular degeneration was lessened, although there was still residual injury present. The vitamin E group had only mild to moderate degeneration and isolated necrotic cells, see Figure 3, while the hydrocortisone group revealed moderate vacuolar degeneration but less frequent necrosis, see Figure 4.

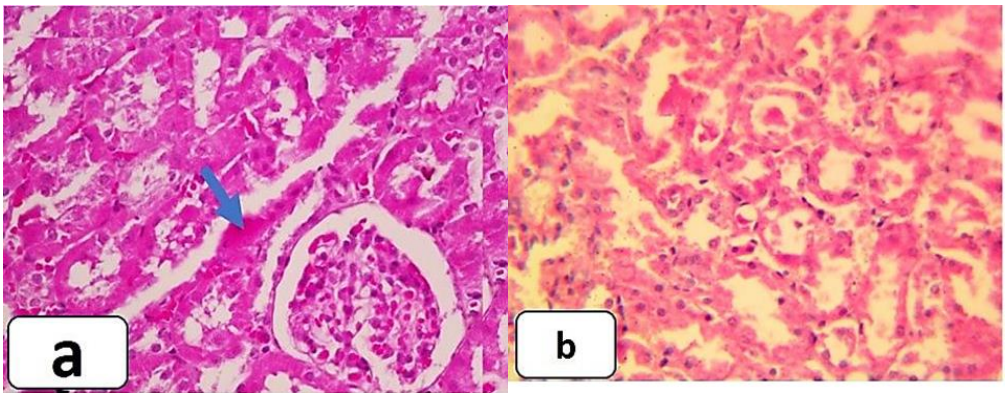

Figure 4. Histopathological section of kidney in the 4th group (vitamin E treatment) showed: (a) Tubular epithelial degeneration with focal necrotic cells; (b) degeneration, necrosis, and desquamation of epithelium of renal tubules (H &E, ×400).

Among all treated groups, the combination treatment group showed the highest protective power. The renal tissue architecture was almost normal, similar to that in the Sham group, with no evident signs of tubular swelling, necrosis, or hemorrhage, see Figure 5.

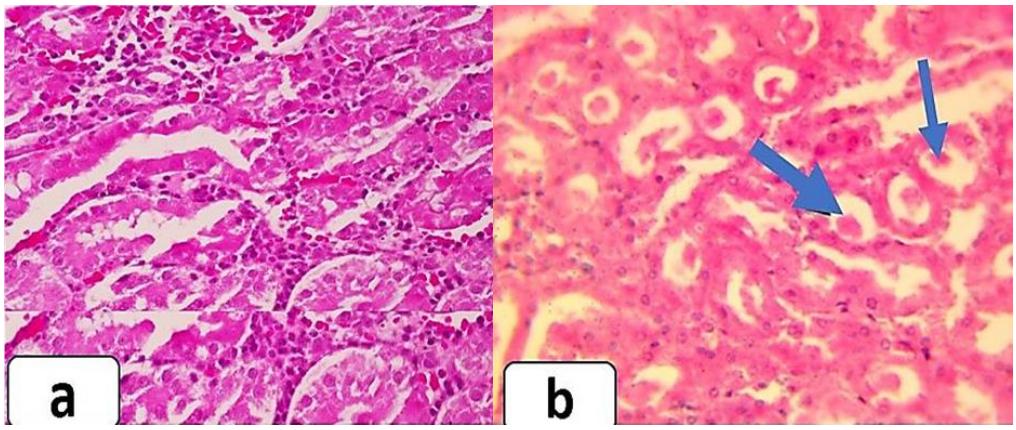

Figure 5. Histopathological section of kidney in the 5th group (cydrocortisone treatment) showed: (a) Moderate tubular epithelial degeneration; (b) hyaline casts in tubular epithelium (arrows) with partial preservation of glomerular structure (H &E, ×400).

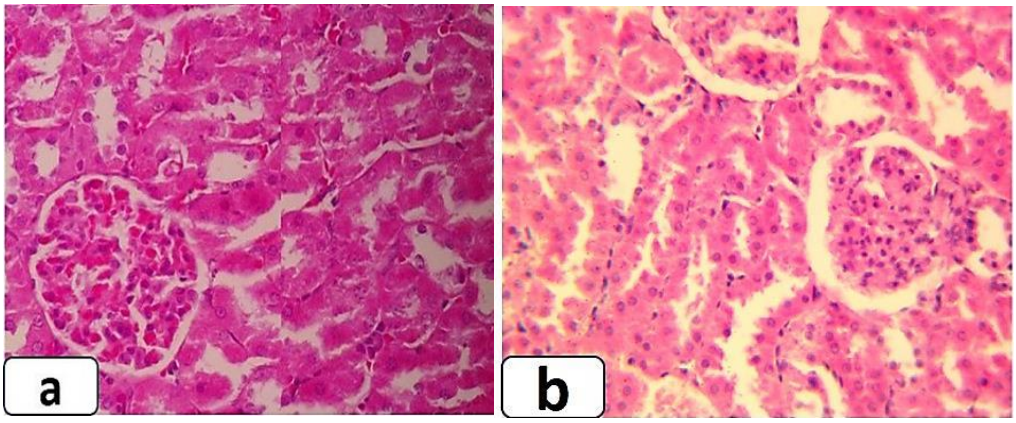

Figure 6. Histopathological section of the kidney in the 6th group (combination treatment) showed: The kidney shows preserved normal histologic structure (H & E, ×400).

Histopathological Scores

Compared with the sham group, the ischemia-reperfusion group had obviously higher scores of tubular degeneration (TD), tubular necrosis (TN), tubulointerstitial inflammation (TIN), and total histological score (THS) ($p>0.05$).

- Tubular degeneration was significantly reduced in the treatment groups, including vitamins C and E, hydrocortisone, in comparison to the ischemia-reperfusion group.
- Tubular necrosis scores: significantly lower in vitamin C, hydrocortisone, and combination groups the greatest reduction observed being the combination and vitamin C groups.
- TIN scores did not differ significantly among treatment groups compared to Sham and ischemia-reperfusion groups ($p>0.05$).
- THS values were significantly lower in all treatment groups compared to ischemia-reperfusion, with the lowest scores observed in combination and vitamin C groups.
- Comparison among the treated groups showed that
- The vitamin E group exerted significantly higher TD, TN, and THS as compared to groups of vitamin C and combination, suggesting a poor protective effect.
- Combination and vitamin C treatments had the most pronounced reno-protective effects, with vitamin E showing the least improvement.

Table 4. Histopathological scores of TD, TN, TIN, and THS (present as median and range).

Group	G1	G2	G3	G4	G5	G6
Tubular Degeneration	0 (0)	3 (3–4)[a]	1 (1–2)[ab]	2 (1–2)[ab*]	1 (1–3)[ab]	1 (0–1) [ba*]
Tubular Necrosis	0 (0)	3 (2–3)[a]	0 (0) [b♣]	1 (0–1) [ab*♣]	0 (0–1)[b]	0 (0) [b*]
Tubulointerstitial nephritis	0 (0)	1 (0–1) [a]	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
THS	0 (0)	5 (4–5.5) [a]	0.5 (0.5–1) [ab♣]	1.5 (1–2) [ba*♣]	0.5 (0.5–3) [ab]	0.5 (0–1) [ba*]

Table 5. Summary of Key Consequences.

Group	Protective Effect
Combination	Most effective
Vitamin C	Strong protective effect
Hydrocortisone	Moderate protection
Vitamin E	Least protective
Ischemia-reperfusion	Severe injury
Sham	Normal

4. Discussions

In this regard, the impact of the present study revealed that renal ischemia-reperfusion injury was characterized by marked tubular epithelial degeneration, necrosis, vascular congestion, and inflammatory infiltration, in agreement with the established role of oxidative and inflammatory mechanisms in the pathology of ischemia-reperfusion injury [14], [15], [16]). As highlighted, proximal tubular cells are highly sensitive to ischemic insult, which is in line with the prominent structural injury presented in the untreated ischemia-reperfusion group here. Vitamin C administration decreased tubular injury and necrosis significantly. This also agrees with its reported role in scavenging ROS, regenerating other antioxidants, and maintaining endothelial integrity during reperfusion

[17], [18], [19], [20]. Recent studies have similarly reported that vitamin C improves renal microcirculation and reduces oxidative biomarkers in experimental ischemia-reperfusion models [21], [22], [23], [24].

Vitamin E supplementation also provided a protective effect, but less pronounced. This perhaps illustrates the necessity for synergistic interaction of lipid-soluble and water-soluble antioxidant systems because vitamin E has to be regenerated by vitamin C for sustainable maximal antioxidant function [25], [26], [27], [28]. Similarly, previous and recent studies have also noted that vitamin E supplementation alone confers only partial structural protection as compared to combined antioxidant therapy [29], [30], [11]. The improvement in renal architecture by hydrocortisone was moderate, which supports the known pharmacological roles of hydrocortisone in mitigating cytokine-driven inflammation, leukocyte infiltration, and microvascular damage during reperfusion [31], [32], [33], [34]. However, its inability to directly neutralize ROS may explain why its protective effect was less complete than antioxidant therapy [35], [36], [37].

The most significant reno-protective effect was observed in the combination therapy group. This supports our key hypothesis states that simultaneously targeting oxidative stress via vitamins C and E and inflammation via hydrocortisone offers superior protection in renal ischemia-reperfusion injury [38], [39]. Similar synergistic protection has been reported in recent experimental ischemia-reperfusion research, underlining the advantage of multimodal therapy [9], [40], [41].

5. Conclusions

Overall, this study confirms that renal ischemia-reperfusion injury originates from interrelated oxidative and inflammatory processes and points out that combination therapy has an advantage compared with single-agent treatment. These results indicate possible translational application in perioperative and transplant-related renal protection. Also, this study suggests that combined antioxidant and anti-inflammatory therapy may represent a promising strategy for minimizing renal ischemia-reperfusion injury. Such therapeutic approaches might have clinical relevance in renal transplantation, cardiac surgery, and acute kidney injury conditions.

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