The New Journal of Urology
eISSN 3023-6940
doi: https://doi.org/10.33719/nju1631647

RESEARCH ARTICLE

Evaluation of Human Serum Albumin's Potential Effects on Renal Ischemia-Reperfusion Injury in a Rat Model

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Submitted: *2025-02-02*
Accepted: *2025-08-08*

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Abstract

Objective: The purpose of this study is to examine how acute ischemia-reperfusion injury (IRI) in a rat model is affected by replacing human serum albumin (HSA).

Material and Methods: Thirty-six male Wistar albino rats were randomly divided into six groups: Control, Ischemia, Ischemia-Reperfusion (IR), Placebo, Preoperative Albumin (A1), and Intraoperative Albumin (A2). The renal artery of the kidney was blocked using 3/0 silk sutures to induce ischemia, followed by one hour of reperfusion in certain groups. The A1 group received 20% HSA (2.5 g/kg intraperitoneally) 24 hours before surgery, while the A2 group received the same dose 30 minutes before reperfusion. Samples of kidney and blood tissue were gathered for immunohistochemical, histological, and biochemical assessments. Biochemical parameters included ischemia-modified albumin (IMA), total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI). Histological assessments measured cortical and medullary damage, while immunohistochemistry evaluated oxidative stress markers such as superoxide dismutase (SOD1), glutathione reductase (GSR), and myeloperoxidase (MPO).

Results: Biochemical analyses showed no significant differences in TOS, TAS, OSI, and IMA levels between groups. Histological evaluation revealed that the A2 group had reduced kidney damage, particularly in the medulla, compared to the ischemia and placebo groups. Immunohistochemical findings indicated minor differences in oxidative stress marker expression, though not statistically significant.

Conclusion: Intraoperative HSA replacement has the potential to reduce ischemia-induced renal injury in rats, especially in medullary tissues. These findings suggest that HSA may be a promising therapeutic agent for managing ischemic kidney damage during partial nephrectomy. Further clinical studies are needed to validate its efficacy and safety in human applications.

Keywords: human serum albumin, ischemia-reperfusion injury, oxidative stress, rat model, renal ischemia

Cite; Yildirim U, Uslu M, Ezer M, Erihan IB, Kahraman AA, Bingol SA. Evaluation of Human Serum Albumin's Potential Effects on Renal Ischemia-Reperfusion Injury in a Rat Model. New J Urol. 2025;20(3):130-138. **doi:** https://doi.org/10.33719/nju1631647

INTRODUCTION

Renal cell carcinoma (RCC) is the seventh most common type of cancer globally, with approximately 350,000 new cases diagnosed annually (1). The incidence of RCC has increased sharply, especially in the past 50 years. This rise can be attributed to advancements in medical imaging technologies such as magnetic resonance imaging and computed tomography. These remarkable improvements in diagnostic equipment have also enhanced the variety and success of treatment methods (2). The guidelines of the European Association of Urology recommend partial nephrectomy (PN) for tumors classified as T1 (localized) in the TNM tumor staging system (3,4). During PN, it is often necessary to temporarily clamp the vessels supplying blood flow to the kidney to delineate tumor margins better, clearly visualize the tumor base, and prevent excessive bleeding. Even though this interruption in blood flow is temporary, the ischemic damage to the kidney can result in permanent loss of function (5).

Reactive oxygen species (ROS) generated by mitochondria are temporarily increased when the kidney is reperfused or ischemic, which sets off pro-inflammatory processes. Among other pathogenic processes, excessive ROS production by mitochondria damages cellular components and activates various acute injury mechanisms that jeopardize kidney function (6). Numerous studies in the literature have been conducted to minimize ischemia-reperfusion injury (IRI) caused by warm ischemia applied to the kidney during PN (7,8). Previous studies have clearly demonstrated that human serum albumin (HSA) is one of the primary antioxidant components in the body that combats ROS (9). Superoxide dismutase-1 (SOD1), myeloperoxidase (MPO), and glutathione reductase (GSR) are significant indicators of oxidative stress. SOD1 prevents oxidative damage by converting superoxide radicals into hydrogen peroxide and oxygen, and hence plays a central role in cellular defense systems. MPO, an enzyme found primarily in neutrophils, has a function in the formation of reactive oxygen species and is regarded as a key marker in inflammatory responses. GSR helps to maintain cellular redox homeostasis by supporting the glutathione cycle. Assessment of the expression and activity levels of these proteins gives essential information in evaluating the extent of oxidative stress and damage in renal tissue (10–12). However, according to our literature review, the effects of HSA replacement on renal IRI have not yet been investigated in rat models. No human studies have been identified on this subject either.

This study aims to investigate the potential effects of HSA replacement on acute IRI in a rat model and to shed light on future human studies on this subject.

MATERIALS AND METHODS

Animals

This current research was conducted at Kafkas University Laboratory Animal Center following the "Guide for the Care and Use of Laboratory Animals." Ethical approval for the project was obtained from the Kafkas University Animal Research Local Ethics Committee (decision date/number: 01-03-2023/2023-021). This study was funded by the Kafkas University Scientific Research Projects Unit (Project number: 2023-TS-58). A total of 36 male Wistar albino rats (aged 8–12 weeks, weighing 180–260 grams) were used in the study. The rats were housed with ad libitum food access in a room maintained at 22 ± 2°C with a 12-hour light-dark cycle.

Groups

The rats were randomly divided into six equal groups:

Control group: Nephrectomy was performed on healthy kidney tissue after anesthesia.

Ischemia group: One kidney was subjected to ischemia for one hour after anesthesia, and the damaged kidney was then removed. Although a separate sham group was not used, the control group underwent both anesthesia and nephrectomy without ischemia, reflecting both healthy renal tissue and surgical stress response. Thus, it served the functional purpose of a sham group.

IR group: One kidney underwent one hour of ischemia followed by one hour of reperfusion after anesthesia. The kidney tissue was removed after completing the reperfusion phase.

Placebo group: The procedure included one hour of ischemia followed by one hour of reperfusion. The rats were administered 12.5 ml/kg saline intraperitoneally 24 hours before surgery. At the conclusion of the reperfusion phase, kidney tissue was extracted.

Preoperative albumin (A1) group: The procedure included one hour of ischemia and one hour of reperfusion. The rats were given 2.5 g/kg of 20% HSA (12.5 ml/kg) intraperitoneally 24 hours before surgery (13, 14). At the conclusion of the reperfusion phase, kidney tissue was extracted.

Intraoperative albumin (A2) group: The procedure included one hour of ischemia and one hour of reperfusion. The rats were administered 2.5 g/kg of 20% HSA (12.5 ml/kg) intraperitoneally 30 minutes before the start of reperfusion. Kidney tissue was removed after the reperfusion period.

Anesthesia

Rats were given intramuscular injections of 90 mg/kg ketamine (Keta-Control®, Doa Pharmaceuticals) and 10 mg/kg xylazine (Vetaxyl®, Vet-Agro) to induce anesthesia (15). The procedures were carried out with constant monitoring and careful management of anesthesia, ensuring the well-being of the animals throughout the process.

Surgical Procedure

Following the induction of anesthesia, all rats were positioned in the supine position, and the surgical site was shaved and disinfected. An abdominal incision measuring 2 cm was performed. The renal artery of the kidney was blocked using 3/0 silk sutures to induce ischemia, and then the abdomen was closed. To achieve reperfusion, the surgical team reopened the abdominal cavity, removed the sutures around the renal artery, and then closed the abdomen again. Following the restoration of blood flow, the abdominal cavity was surgically accessed, and samples of tissue and blood were obtained. At the end of the entire experimental phase, the animals were responsibly sacrificed via decapitation while under deep anesthesia.

Biochemical Analyses

Serum samples were assessed to determine ischemia-modified albumin (IMA), total oxidant status (TOS), total antioxidant status (TAS), and the oxidative stress index (OSI). The levels of TOS and TAS were quantified using Erel's automated colorimetric method (Rel Assay Diagnostics®, Mega Tıp, Türkiye). TOS results were expressed in μmol H_2O_2 Eq/L, while TAS values were presented in mmol Trolox Eq/L. OSI, an indicator of oxidative stress, was calculated as the ratio of TOS to TAS using the formula μmol [(TOS / (TAS × 1000)) × 100]. IMA concentrations were measured with a colorimetric approach (Rel Assay Diagnostics®, Mega Tıp, Turkey) and a spectrophotometer, with outcomes reported in u/L.

Histological Analyses

Following the experimental procedures, kidney tissues were preserved in 10% formalin and embedded in paraffin blocks. Serial sections of 5 μm thickness were cut using a microtome (Leica RM2125RTS). The sections were stained with hematoxylin-eosin (H&E), and images were captured using a light microscope (Olympus BX53, Tokyo, Japan). Each kidney was evaluated using two slides, and five fields per slide were analyzed under 20x magnification for scoring. The cortex and medulla were scored separately (0: none, 1: mild, 2: moderate, 3: severe). Total tissue damage was calculated by summing the scores.

Cortical damage was assessed by evaluating cellular changes in Bowman's capsules, distal tubules, and proximal tubules. Medullary damage was assessed by examining debris and hemorrhage in descending and ascending Henle's loops and the tubules.

Immunohistochemical (IHC) evaluations were performed using avidin-biotin-peroxidase complex (ABC) staining. Polyclonal MPO primary antibody (Elabscience, E-AB-10466, 1/50), polyclonal GSR primary antibody (Elabscience, E-AB-14115, 1/50), and polyclonal SOD1 primary antibody (Cloud-Clone, PAB960Ra01, 1/50) were used for IHC staining. Images were acquired with a light microscope (Olympus BX53, Tokyo, Japan). Each animal was assessed using two slides and five fields, and the immunoreactivity intensities of kidney histological structures (glomerulus, Bowman's capsule, urinary space, vascular space, distal tubule, and proximal tubule in the cortex) were determined.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro-Wilk test. Descriptive statistics were presented as mean ± standard deviation (SD) for normally distributed data and as median with interquartile range (IQR) for non-normally distributed or ordinal data. For comparisons between multiple groups, one-way ANOVA was applied for

normally distributed variables; when a significant difference was detected, post hoc pairwise comparisons were performed using Tukey's Honestly Significant Difference (HSD) test. The Kruskal-Wallis test was used for multiple comparisons of non-normally distributed or ordinal data. When a significant difference was detected, post hoc pairwise comparisons were performed using the Dunn-Bonferroni test to control the Type I error rate.

A two-tailed p-value of less than 0.05 was considered statistically significant. Exact p-values (e.g., p=0.032) were reported rather than threshold values. Effect sizes (e.g., eta squared for ANOVA or Cohen's d for pairwise comparisons) were not calculated due to the unavailability of raw data.

RESULTS

Biochemical findings

Table 1 displays the outcomes of biochemical testing. No statistically significant differences were observed in TAS, TOS, OSI, and IMA levels between paired groups. Although a statistical difference in TAS values was found among multiple groups in one-way ANOVA testing, post-hoc analysis revealed no significant differences between any two groups.

Histological Findings

Histological examinations included two slides per animal and five fields per slide. Histological images of each group are shown in Figure 1.

In the renal cortex, damage to Bowman's capsules was similar across all groups. Proximal tubule damage was higher in the ischemia group than in the other groups, while distal tubular damage was similar across the groups. When overall cortical damage was assessed, the ischemia group showed the highest degree of damage. The least damage was observed in the control group, with the intraoperative albumin-treated group displaying damage levels closer to the control group (Figure 1, A1–6).

In the renal medulla, damage to descending and ascending Henle's loops and tubular debris/hemorrhage was significantly higher in the ischemia group. Damage in the IR group was close to the ischemia group, while all other groups exhibited significantly lower levels of damage (Figure 1, B1–6).

Table 2 displays the results of the histological evaluations. Cortical damage did not differ significantly between the groups. Group A2 showed significantly less medullary damage than the ischemia group (p = 0.001). While group A1 performed better than the ischemia group, the differences were not statistically significant. When all groups were evaluated together for total damage, a statistically significant difference was detected (p=0.009). However, no significant differences were found between individual group pairs in post hoc pairwise comparisons.

Immunohistochemical Findings

Immunohistological analyses included two slides per animal and five fields per slide. Immunohistochemical images for each group are shown in Figure 1 (C-D-E).

Table 1. Comparisons of biochemical findings between groups (mean ± SD).

Groups	TAS (mmol/L)	TOS (µmol/L)	OSI	IMA (u/L)
Control	2.67 ± 0.52[a]	25.33 ± 5.35[a]	0.97 ± 0.24[a]	184.47 ± 50.14[a]
Ischemia	1.04 ± 0.84[a]	22.71 ± 10.88[a]	4.24 ± 3.71[a]	209.64 ± 146.28[a]
IR	1.05 ± 1.03[a]	23.68 ± 16.03[a]	4.55 ± 3.79[a]	272.68 ± 200.50[a]
Preop Albumin (A1)	0.88 ± 0.93[a]	26.67 ± 3.01[a]	6.65 ± 4.18[a]	154.65 ± 25.10[a]
Intraop Albumin (A2)	1.15 ± 1.01[a]	13.86 ± 5.44[a]	2.76 ± 3.82[a]	104.70 ± 121.93[a]
Placebo	0.83 ± 1.13[a]	19.25 ± 9.42[a]	5.12 ± 4.02[a]	169.53 ± 107.17[a]
p-value	0.016	0.223	0.139	0.309

TAS: total antioxidant status, TOS: total oxidant status, OSI: oxidative stress index, IMA: ischemia-modified albumin, IR: ischemia-reperfusion, *p-value*: *One-way ANOVA*, SD: Standard Deviations, [a]: Different superscripts in the same column indicate statistical differences between groups (*post-hoc Tukey HSD p≤0.0033*).

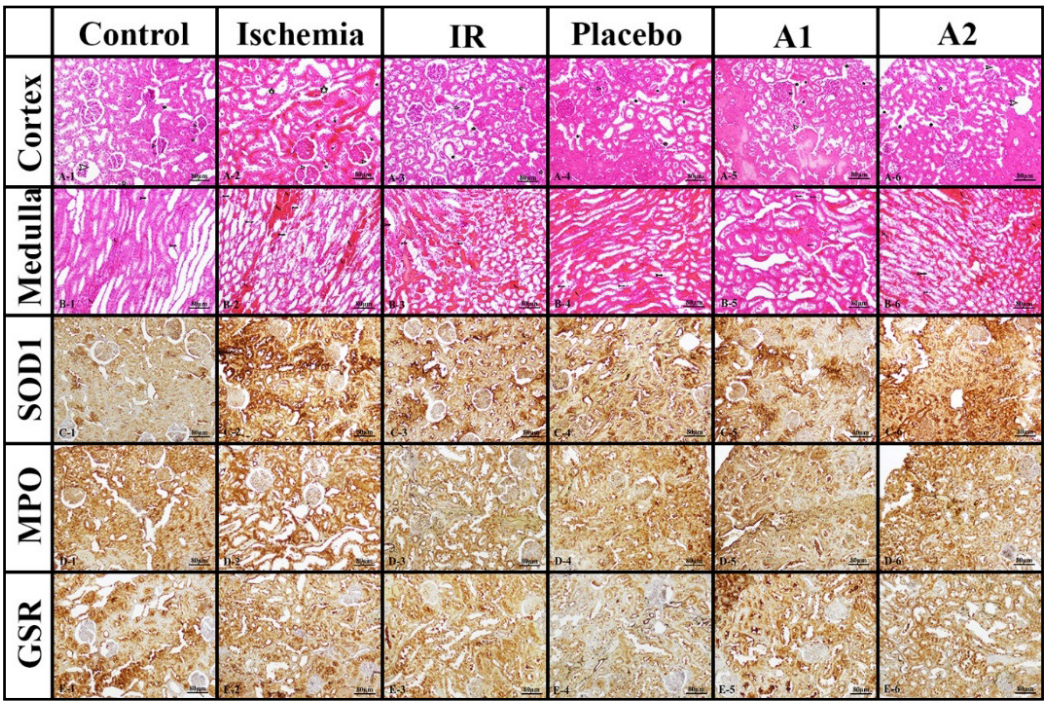

Figure 1. A. Cortex H&E staining (Arrowhead: Glomerular damage, Leaf: Tubulus Distalis damage, Star: Tubulus Proksimalis damage), A1-6, 20x (80µm). B. Medulla H&E staining (Arrow: Tubulus damage, Lightning: Hemorrhage), B1-6, 20x (80µm). C. SOD1 immunoreactivity, C1-6, 20x (80µm). D. MPO immunoreactivity, D1-6, 20x (80µm). E. GSR immunoreactivity E1-6, 20x (80µm).

The results of SOD1 immunohistochemistry are presented in Table 3. The highest cortical immunoreactivity for SOD1 was observed in the ischemia and IR groups, while other groups exhibited similar levels. Medullary immunoreactivity was comparable across all groups. When these regions were combined, no significant differences in SOD1 immunoreactivity were detected among the groups (Figure 1, C1–6).

The results of MPO immunohistochemistry are shown in Table 3. The highest cortical immunoreactivity for MPO was observed in the control group. Medullary immunoreactivity was similar across all groups. When both regions were considered together, no significant differences in MPO immunoreactivity were identified among the groups (Figure 1, D1–6).

Table 2. Comparisons of histopathological findings between groups [median (Q1-Q3)].

Groups	Cortex Damage (CD)	Medulla Damage (MD)	Total Damage (CD+MD)
Control	0.0 (0.00-1.125)[a]	0.50 (0.375-0.625)[ab]	0.50 (0.375-2.00)[a]
Ischemia	0.75 (0.50-1.00)[a]	2.00 (1.875-3.00)[b]	3.00 (2.375-3.625)[a]
IR	0.50 (0.375-1.50)[a]	1.00 (0.0-1.50)[ab]	1.50 (0.375-3.00)[a]
Preop Albumin (A1)	0.50 (0.0-1.25)[a]	0.50 (0.0-0.50)[ab]	0.75 (0.50-1.625)[a]
Intraop Albumin (A2)	0.50 (0.0-0.75)[a]	0.0 (0.0-0.50)[a]	0.50 (0.50-0.75)[a]
Placebo	0.50 (0.375-1.625)[a]	0.75 (0.375-1.00)[ab]	1.00 (0.875-2.625)[a]
p-value	0.703	0.002	0.009

p-value: *Kruskal wallis*. [a,b]: Different superscripts in the same column indicate statistical differences between groups (*post-hoc Dunn-Bonferroni test, p≤0.0033*). (MD: Ischemia-A2 p=0.001).

Table 3. Comparisons of total CAT, XDH, and GPX1 immunoreactivity between groups [median (Q1-Q3)].

Groups	SOD1	MPO	GSR
Control	0.0 (0.0-0.625)[a]	1.25 (0.375-2.00)[a]	1.00 (0.875-1.625)[a]
Ischemia	0.25 (0.0-1.125)[a]	0.75 (0.50-1.00)[a]	0.75 (0.375-1.125)[a]
IR	0.25 (0.0-1.125)[a]	0.50 (0.375-1.125)[a]	0.75 (0.0-1.50)[a]
Preop Albumin (A1)	0.25 (0.0-0.625)[a]	0.50 (0.375-1.00)[a]	0.75 (0.0-1.125)[a]
Intraop Albumin (A2)	0.25 (0.0-0.75)[a]	0.50 (0.375-1.00)[a]	0.75 (0.50-1.125)[a]
Placebo	0.50 (0.0-0.625)[a]	0.50 (0.375-1.00)[a]	0.75 (0.50-1.125)[a]
p-value	0.965	0.618	0.740

SOD1: superoxide dismutase, MPO: myeloperoxidase, GSR: glutathione reductase, IR: ischemia-reperfusion, *p-value*: *Kruskal wallis*. [a]: Different superscripts in the same column indicate statistical differences between groups (*post-hoc Dunn-Bonferroni test, p≤0.0033*).

The results of GSR immunohistochemistry are also provided in Table 3. The highest cortical immunoreactivity for GSR was found in the control group. Medullary immunoreactivity was comparable among all groups. When both regions were combined, no significant differences in GSR immunoreactivity were observed among the groups (Figure 1, E1–6).

DISCUSSION

The key finding of the presented study is that intraoperative HSA showed a potential for reducing ischemic damage in the kidney in a rat model. While this reduction was statistically significant in some groups, it was not significant in others. Although preoperative intraperitoneal administration allows more time for systemic absorption, the peak plasma concentration may occur too early, potentially declining before the critical reperfusion phase. In contrast, intraoperative administration provides a synchronized antioxidant effect exactly at the onset of reperfusion, which may explain its superior protective outcome despite lower cumulative plasma exposure (16,17).

The impact of albumin on ischemia-reperfusion injury (IRI) in different rat model tissues has been the subject of several investigations. Watts and Maiorano showed that minimal levels of albumin replacement significantly reduced myocardial damage caused by ischemia and reperfusion in rats, likely through antioxidant mechanisms (18). Sampaio de Holanda and colleagues provided direct evidence in their research that sulforaphane and albumin reduced intestinal IRI. They proposed that the antioxidant abilities of albumin may be responsible for this decrease. (19). Tang et al. studied the impact of HSA on global cerebral ischemia injury in rats and discovered that HSA therapy could mitigate early neuronal damage through Wnt/β-catenin/ROS signaling pathways (20). Last but not least, in a study conducted on ischemic rat ovaries, HSA alleviated tissue damage caused by IRI. Similar to our study, HSA was also administered intraperitoneally in this research, which is significant and supports our findings (14).

The effects of various active substances on IRI in rat kidneys have been previously studied using biochemical markers such as TAS, TOS, and IMA. Compared to the placebo group, TAS levels in the treatment groups were significantly higher in several of these studies, while TOS levels were significantly lower. Significant differences in IMA levels between groups were also reported in a number of studies (21–24). In our study, although not statistically significant, TAS levels were found to be higher in the A2 group compared to the placebo group. Similarly, we found that TOS levels in the A2 group were lower than those in the placebo group, but the difference was again not statistically significant.

Research has also examined renal IRI in a rat model utilizing albumin-enriched nanocomplexes. An albumin-enriched nanocomplex was created for the solubilization and intravascular delivery of clopidogrel bisulfate. This study documented the positive impact of the administered nanocomplex on IRI. Nonetheless, it is not possible to discuss the effects of pure albumin in this study, as albumin was primarily used as a carrier protein (25).

Maintaining kidney function after PN is crucial for patients with a single kidney, those diagnosed with chronic kidney failure before surgery, patients with multiple renal masses, and those with a history of proteinuria. Although the goal of PN is to remove the tumor while preserving the surrounding healthy parenchyma, studies have shown an approximately 10% decrease in glomerular filtration rates after surgery. This decrease is influenced by multiple factors, including the type of ischemia used (26). Albumin is among the most prevalent proteins in the mammalian body, with around 40% found in circulating blood. It is a significant constituent of various extracellular fluids, including interstitial fluid, lymph, and cerebrospinal fluid (27). Research indicates that hypoalbuminemia is identified in almost 90% of hospitalized elderly patients, attributable to various sociodemographic variables, including malnutrition (28). The scientific data indicate that the average age of patients diagnosed with kidney tumors exceeds 60, suggesting that most patients are elderly (29). When this information is interpreted, it should be considered that patients undergoing PN for kidney tumors with ischemia may be hypoalbuminemic.

The findings of our research show that HSA may reduce ischemia-induced renal ischemic damage in a rat model. The data obtained may not directly translate to humans; nevertheless, the use of HSA, which is generally an easily supplemented substance, should be evaluated in humans prior to PN. Especially in patients with hypoalbuminemia due to malnutrition or aging, preoperative HSA replacement may have potential benefits. Comprehensive clinical studies involving larger patient groups should be conducted on this subject.

Limitations

This study was conducted using a rat model, and the findings cannot be directly generalized to humans. Without clinical studies conducted on humans, the validity of the results remains limited. Additionally, the number of animals used in the study was limited (36 rats). Larger sample groups could provide stronger and more generalizable results. Although differences were observed among groups in the biochemical results (such as TAS, TOS, OSI, and IMA), these differences did not achieve statistical significance due to the small sample size, making it difficult to assess the effects of the study fully. Another limitation is related to the timing of HSA administration. Although the effects of albumin replacement administered at different time points (preoperatively and intraoperatively) were evaluated, the effects of various doses and timing protocols were not investigated.

Furthermore, the study only evaluated the acute effects of HSA on renal damage. The long-term outcomes of albumin replacement were not examined. In addition, the study's control group was limited to healthy renal tissue. To reduce animal use and maintain ethical standards, the study employed a single control group that sufficiently represented sham conditions by including anesthesia and surgical manipulation without ischemia or reperfusion. The potential effects of other possible control groups (e.g., different antioxidant treatments) were not investigated.

Although the present study has certain limitations, we believe that the results will still guide future research. This study is pioneering in its field and examines a topic with high clinical applicability.

CONCLUSION

In a rat model, human albumin has the potential to reduce renal parenchymal ischemia injury, particularly when administered intraoperatively. To verify these findings in humans, further clinical trials with a wider range of patient demographics and higher sample sizes are necessary. By expanding our understanding of the role of albumin in renal protection, future studies could pave the way for improved outcomes in kidney surgeries and enhanced postoperative recovery and nephrological health.

Acknowledgement: The authors thank Kafkas University Scientific Research Projects Coordination Unit (TS-2023-58).

Funding: This study was funded by the Kafkas University Scientific Research Projects Coordination Unit.

Conflict of Interest: The author declares that they have no conflicts of interest.

Ethics Committee: Ethical approval for the project was obtained from the Kafkas University Animal Research Local Ethics Committee (decision date/number: 01-03-2023/2023-021).

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