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Reduction in lung injury in an experimental ischemia-reperfusion model with tranexamic acid: A biochemical and histopathological assessment

Muhammet Fethi Sağlam[1], Zerrin Pulathan[2], Süleyman Caner Karahan[3], Esin Yuluğ[4]

[1]Department of Cardiovascular Surgery, Ankara Yıldırım Beyazıt University Faculty of Medicine, Ankara, Türkiye
[2]Department of Cardiovascular Surgery, Karadeniz Technical University Faculty of Medicine, Trabzon, Türkiye
[3]Department of Medical Biochemistry, Karadeniz Technical University Faculty of Medicine, Trabzon, Türkiye
[4]Department of Histology and Embryology, Karadeniz Technical University Faculty of Medicine, Trabzon, Türkiye

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ABSTRACT

Objectives: This study aimed to investigate the effectiveness of tranexamic acid in reducing lung injury associated with ischemia-reperfusion in rats.

Materials and methods: Twenty-three male Sprague-Dawley rats (aged 2-3 months and weighing 250±30 g) were divided into three groups: sham, ischemia-reperfusion (IR) injury, and tranexamic acid (TA) groups. The rats in the IR and TA groups underwent abdominal aortic clamping for 1 h, followed by 2 h of reperfusion. The TA group received 100 mg/kg tranexamic acid intravenously before clamping. Biochemical and histological evaluations were performed.

Results: Compared to those in the sham group, the plasma myeloperoxidase, malondialdehyde, and serum ischemia-modified albumin levels in the IR group were significantly higher, indicating oxidative stress. Compared to those in the IR group, the ischemia-modified albumin levels in the TA group were significantly lower. Histopathological analysis revealed lung damage in the IR group, which was reduced in the TA group, although the difference was not significant.

Conclusion: Tranexamic acid reduces oxidative stress and local inflammatory responses, mitigating lung reperfusion injury. However, further studies are needed to explore its efficacy in different models and at different doses.

Keywords: Inflammation, ischemia-reperfusion injury, lung injury, oxidative stress, tranexamic acid.

Ischemia is the temporary reduction or cessation of blood flow to a tissue, and reperfusion is the restoration of blood flow.[1] This reduction in blood flow causes tissue damage depending on the duration of ischemia and tissue properties.[2,3] Reperfusion can lead to necrosis, tissue edema, and systemic damage, potentially causing multiple organ failure.[4]

Despite surgical advancements, ischemia-reperfusion (IR) injury remains a key issue in cardiovascular surgery as it can occur after abdominal aortic surgery, emboli, thrombosis, and arterial injuries.[5-7]

The pathogenesis of IR involves tissue injury triggering systemic reactions, neutrophil activation, cytokine release, and the formation of radicals and proteases.[8] In ischemic tissues, blood stasis and hypoxia cause endothelial damage and thrombosis. During reperfusion, tissue plasminogen activator activates plasmin, increasing tissue destruction. Fibrin degradation products block capillaries, affecting distant organs such as the lungs.[9,10]

Studies on IR injury often use chemicals to suppress neutrophils, but research on antifibrinolytic agents is limited.[11,12] These studies show the effects of ischemia and reperfusion on organs, but the pathology is not fully understood.[13-15] Studies show that damage to

Corresponding author: Muhammet Fethi Sağlam, MD. Ankara Yıldırım Beyazıt Üniversitesi Tıp Fakültesi, Kalp ve Damar Cerrahisi Anabilim Dalı, 06800 Çankaya, Ankara.
E-mail: dr.m.fethisaglam@gmail.com

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reperfused tissues and organs is caused by neutrophil products.[10,11] Suppressing neutrophils can prevent damage, indicating a need for further study. Hence, this study aimed to investigate the effect of tranexamic acid (TA) on damage to distant organs caused by aortic ischemia and reperfusion in rats.

MATERIALS AND METHODS

This study utilized 23 healthy male Sprague-Dawley rats (aged 2-3 months and weighing 250±30 g) bred in the laboratory of Karadeniz Technical University Faculty of Medicine. The temperature in the housing and experimental environment was maintained between 20°C and 26°C. The rats were fasted for 12 h before the experiment. The study protocol was approved by the Local Ethics Committee for Animal Experiments of Karadeniz Technical University Faculty of Medicine (date: 18.03.2009, no: 2009/243/1). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Analgesia and anesthesia were achieved by intraperitoneally administering xylazine hydrochloride (Rompun; Bayer AG, Leverkusen, Germany) and ketamine hydrochloride (Ketalar; Pfizer Inc., New York, NY, USA) to the rats in the laboratory. The rats were weighed using an electronic scale, and their weights were recorded. The midline of the abdomen and the anterior neck region were shaved. Under a microscope, a transverse incision was made in the anterior neck region. The left carotid artery and right internal jugular vein were explored and cannulated. The arterial line was connected to a monitor (4113-K Model; Nihon-Kohden, Tokyo, Japan) using a three-way stopcock and transducer set.

After catheterization and monitorization, a median laparotomy was performed by dissecting the skin, subcutaneous tissue, and muscle tissue in the midline of the abdomen. The retroperitoneal region was opened, and the abdominal aorta was explored. After exploration, all subjects received heparin (Nevparine; Mustafa Nevzat İlaç Sanayi A.Ş., İstanbul, Türkiye) to achieve anticoagulation. After heparin administration, saline was given to the subjects in IR group, and TA (Transamin-Fako İlaç A.Ş. İstanbul, Türkiye) was administered via a central venous catheter to the subjects in TA group. In IR and TA groups, the abdominal aorta was clamped with a bulldog clamp at the infrarenal level to induce aortic ischemia. Ischemia was confirmed by the absence of a pulse distal to the clamp, which was also verified by a handheld Doppler device. The ischemia period lasted for 60 min.

In IR and TA groups, the aortic clamp was removed after 1 h of ischemia, and reperfusion was initiated. The revascularization of the previously ischemic areas was confirmed by the return of palpable femoral artery pulses and verified using a handheld Doppler device. Reperfusion lasted for 2 h. At the end of the experiment, arterial blood was collected from the carotid arteries for biochemical analysis, and the rats were then euthanized.

To determine the effect of TA on lung injury in an experimental aortic IR model, rats were divided into three groups: the sham (control) group (n=9), the IR group (n=7), and the TA group (n=7). In the sham group, laparotomy was performed without inducing IR, and blood and tissue samples were taken at the end of the third hour. In the IR group, laparotomy was performed, and the abdominal aorta was explored. Saline was administered via a central venous catheter before clamping the aorta at the infrarenal level to induce 1 h of aortic ischemia. Following ischemia, the clamp was removed, and reperfusion was maintained for 2 h. Blood and tissue samples were collected at the end of the reperfusion period. In the TA group, laparotomy was performed, and the abdominal aorta was explored. To induce 1 h of ischemia, tranexamic acid was administered via a central venous catheter 5 min before aortic clamping. After the ischemic period, the clamp was released, and reperfusion was maintained for 2 h. Blood and tissue samples were collected at the end of the reperfusion period.

After the experimental process, arterial blood was collected from the carotid artery using a blood gas syringe and a 10 mL syringe. The collected blood was transferred into biochemistry tubes, EDTA (ethylenediaminetetraacetic acid) tubes, and citrate tubes. Median sternotomy was performed to expose the trachea, pericardium, and heart. Both of the pleurae were opened to access the lungs. The left lung was clamped at the main bronchus, and an cannula was inserted into the trachea through the neck region. The tip of the cannula was advanced into the right main bronchus for bronchoalveolar lavage (BAL). Phosphate-buffered saline was

administered to the right lung, and the lavage fluid was aspirated and transferred to biochemistry tubes. This process was repeated, resulting in 4 mL of BAL fluid. The left lung was resected and washed with saline to remove clots and particles, and tissue samples were collected for biochemical analysis. The tissue samples were placed in Eppendorf tubes and kept on ice.

Serum alanine transaminase, lactate dehydrogenase, and D-dimer levels were measured, and lactate dehydrogenase levels were also measured in the BAL fluid. The serum and plasma samples obtained by centrifugation were stored at −80°C. Lung tissues were also stored at −80°C for biochemical analysis. The lung tissues collected for histopathological examination were fixed in 10% formaldehyde and processed for further analysis.

At the end of the experiment, tissue samples were taken from specific parts of the lungs of all rats and fixed in 10% formaldehyde. The tissue fragments were dehydrated through a graded alcohol series and cleared with xylene solution. Paraffin blocks of the tissues were prepared, and 5-µm thick sections were cut with a microtome (Leica RM2255; Wetzlar, Germany). After deparaffinization, the sections were stained with hematoxylin-eosin. Histopathological evaluation was performed by a blinded histologist who was unaware of the study groups. Lung tissue damage was assessed semiquantitatively in five different fields at high magnification (×400) using the following microscopic scoring criteria:[16] Grade 0, normal lung morphology; Grade 1, mild intraalveolar edema and mild inflammatory cell infiltration; Grade 2, moderate alveolar edema and moderate inflammatory cell infiltration; Grade 3, severe alveolar edema, severe inflammatory cell infiltration, and focal hemorrhage; Grade 4, diffuse inflammatory cell infiltration and damage to the alveolar structure. Each specimen was scored on a scale of 0 to 4. The mean histological score was calculated for each group.

Statistical analysis

Data were analyzed using the NCSS (Number Cruncher Statistical System) 2007 (NCSS LLC., Kaysville, UT, USA) package. Descriptive statistical methods (mean and standard deviation) were used to summarize the data. The distribution of the variables was assessed with the Shapiro-Wilk normality test. For normally distributed variables, one-way analysis of variance was used for intergroup comparisons. For nonnormally distributed variables, the Kruskal-Wallis test was used for intergroup comparisons. When significant differences were found, post hoc analyses were conducted using the Bonferroni-corrected Mann-Whitney U test to identify specific group differences. A p-value <0.05 was considered statistically significant.

RESULTS

Significant differences were observed in plasma myeloperoxidase (MPO) and malondialdehyde (MDA) levels between the sham and IR groups (p=0.001 for both comparisons) and between the sham and TA groups (p=0.001 for both comparisons), indicating increased inflammation and oxidative stress markers in these groups (Table 1).

Significant differences in tissue MPO and MDA levels were observed between the sham and IR groups

Table 1
Plasma parameters

	Sham group (n=9)	IR group (n=7)	TA group (n=7)	Sham *vs.* IR	Sham *vs.* TA	IR *vs.* TA
	Mean±SD	Mean±SD	Mean±SD	*p*	*p*	*p*
Plasma TAFI	41.56±27.46	50.00±22.82	44.55±10.31	0.53	0.79	0.65
Plasma TAT	2.87±0.14	3.06±0.25	3.07±0.22	0.12	0.11	0.95
D-dimer	0.23±0.04	0.27±0.07	0.27±0.04	0.34	0.28	0.92
Plasma MPO	1690.52±332.34	2795.87±374.96**	2551.23±476.90**	0.001*	0.001*	0.18
Plasma MDA	0.31±0.04	0.43±0.04**	0.46±0.04**	0.001*	0.001*	0.27

SD: Standard deviation; IR: Ischemia-reperfusion; TA: Tranexamic acid; TAFI: Thrombin-Activatable Fibrinolysis Inhibitor; TAT: Thrombin-Antithrombin Complex; MPO: Myeloperoxidase; MDA:Malondialdehyde; * p<0.05 *vs.* the IR group; ** p<0.05 *vs.* Sham group.

Table 2
Tissue parameters

	Sham group (n=9)	IR group (n=7)	TA group (n=7)	Sham *vs.* IR	Sham *vs.* TA	IR *vs.* TA
	Mean±SD	Mean±SD	Mean±SD	*p*	*p*	*p*
Tissue MPO	3533.76±219.32	3981.59±164.44**	4068.98±233.62**	0.001*	0.001*	0.23
Tissue MDA	4.52±0.13	5.66±0.48**	4.85±0.58*	0.001*	0.15	0.006*

SD: Standard deviation; IR: Ischemia-reperfusion; TA: Tranexamic acid; MPO: Myeloperoxidase; MDA: Malondialdehyde; * p<0.05 *vs.* IR group; ** p<0.05 *vs.* Sham group.

(p=0.001 for both comparisons) and between the sham and TA groups (p=0.001 for both comparisons), indicating increased levels of neutrophil activity and lipid peroxidation in these groups. Compared to those in the IR group, the tissue MDA levels in the TA group were significantly lower (p=0.006), suggesting that TA may help mitigate lipid peroxidation (Table 2).

Significant differences in serum ischemia-modified albumin (IMA) levels were detected between the sham and IR groups (p=0.007) and between the IR and TA groups (p=0.001), indicating varying levels of IMA (Table 3).

Significant differences were observed in partial pressure of carbon dioxide between the IR and TA groups (p=0.03) and in histological scores between the sham and IR groups (p=0.008) and the sham and TA groups (p=0.012), indicating varying levels of respiratory function and histological damage (Table 4).

Table 3
Serum parameters

	Sham group (n=9)	IR group (n=7)	TA group (n=7)	Sham *vs.* IR	Sham *vs.* TA	IR *vs.* TA
Parameters	Mean±SD	Mean±SD	Mean±SD	*p*	*p*	*p*
Serum IMA	0.44±0.03	0.51±0.03*	0.42±0.04**	0.007*	0.62	0.001*
Serum ALT	70.66±21.23	99.14±49.71	61.57±11.85	0.14	0.57	0.09
Serum LDH	882.00±521.22	933.42±441.73	770.28±344.26	0.78	0.57	0.53
BAL-LDH	657.55±424.39	676.85±401.52	801.42±310.81	0.92	0.49	0.46

SD: Standard deviation; IR: Ischemia-reperfusion; TA: Tranexamic acid; IMA: Ischemia-modified albumin; ALT: Alanine transaminase; LDH: Lactate dehydrogenase; BAL: Bronchoalveolar lavage; * p<0.05 *vs.* the IR group; ** p<0.05 *vs.* the Sham group.

Table 4
Arterial blood gas and histological parameters

	Sham group (n=9)	IR group (n=7)	TA group (n=7)	Sham *vs.* IR	Sham *vs.* TA	IR *vs.* TA
Parameters	Mean±SD	Mean±SD	Mean±SD	*p*	*p*	*p*
pH	7.22±0.14	7.18±0.14	7.30±0.03	0.68	0.32	0.17
PO_2	105.68±24.25	79.38±24.84	105.38±30.39	0.05	0.97	0.07
PCO_2	51.43±14.55	70.62±27.57	45.30±11.81*	0.07	0.40	0.03*
HCO_{3-}	21.12±3.05	20.21±3.13	20.08±2.97	0.55	0.45	0.88
BE	–5.50±5.17	–5.31±3.02	–4.84±3.70	0.90	0.65	0.76
SaO_2	94.40±6.42	84.82±20.41	95.50±2.98	0.10	0.82	0.09
Histological score	1.22±1.09	2.85±0.69**	2.71±0.75**	0.008*	0.012*	0.60

SD: Standard deviation; IR: Ischemia-reperfusion; TA: Tranexamic acid; PO_2: Partial pressure of oxygen; PCO_2: Partial pressure of carbon dioxide; HCO_{3-}: Bicarbonate; BE: Base excess; SaO_2: Oxygen saturation; * p<0.05 *vs.* IR group; ** p<0.05 *vs.* Sham group.

Histopathological examination of the lung tissues revealed normal lung tissue in the sham group. In the IR group, widespread leukocyte infiltration, thrombus in the arterioles, significant degeneration in the alveolar structure, and interalveolar hemorrhage were observed. In the TA group, leukocyte infiltration was decreased compared to that in the IR group, and no thrombi were observed in the arterioles. Interalveolar hemorrhage was also reduced compared to that in the IR group, but diffuse interstitial edema was still present. Hematoxylin-eosin-stained lung tissue samples examined under a light microscope are shown in Figure 1.

DISCUSSION

Reperfusion injury is a significant issue observed in various clinical conditions where ischemic tissues and organs are revascularized. Such conditions include thoracic aortic surgery, abdominal aortic surgery, surgical interventions on lower extremity arteries, and organ transplantation.[17,18] While local damage occurs in target organs in these situations, significant damage also occurs in distant organs, particularly the lungs.[19] Lung damage is a significant concern that increases mortality and morbidity.[20,21]

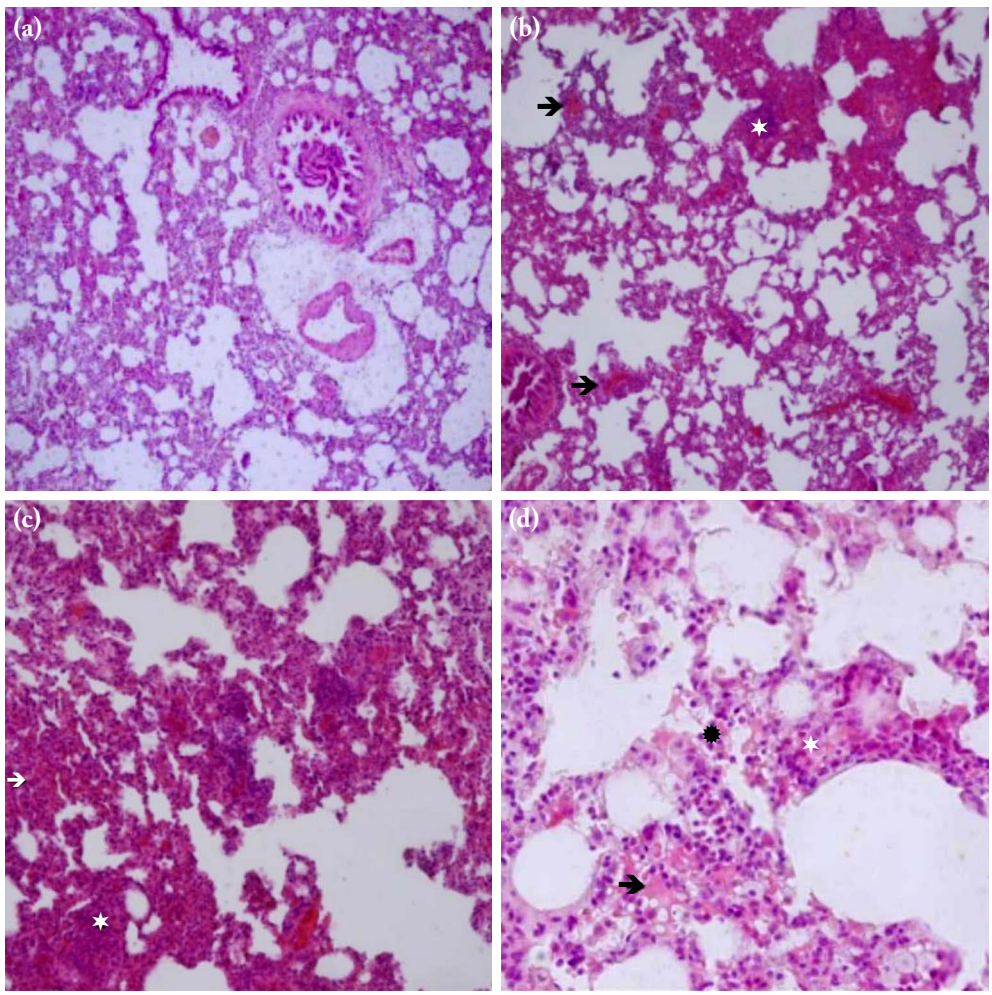

Figure 1. Histological examination of lung tissues. **(a)** Sham group, (H-E, ×100). **(b)** IR group, diffuse leukocyte infiltration (★) and thrombus in arterioles (➔) (H-E, ×100). **(c)** IR group, marked degeneration in alveolar structure (★), interalveolar hemorrhage (➔) (H-E, ×200). **(d)** TA group: Less interalveolar hemorrhage (★), damage to the alveolar structure (✹) and widespread interstitial edema (➔) compared to IR group (H-E, ×200).
IR: Ischemia-reperfusion; TA: Tranexamic acid.

The primary pathogenic factor in reperfusion injury is the generation of free radicals in tissues revascularized after ischemia. These free radicals cause necrosis by damaging cellular structures, particularly through lipid peroxidation of cell membranes. The main source of these free radicals is the neutrophils activated during this process.[22] Neutrophils activated during reperfusion at the site of local damage play a role in both local and distant organ damage. These neutrophils secrete various mediators, such as interleukin (IL)-2, IL-6, IL-8, and tumor necrosis factor-alpha, activating other circulating neutrophils and inflammatory cells, leading to a systemic inflammatory response. This systemic response causes tissue edema and destruction in distant organs due to neutrophilic inflammation.[5,12]

Our study aimed to evaluate the antifibrinolytic and anti-inflammatory effects of TA on stabilizing microthrombi in ischemic tissue and preventing the proinflammatory effects of fibrin degradation products. Our findings indicate that TA has a significant effect in this regard. The inhibitory effects of TA on leukocyte proteinases and its anti-inflammatory effects, as mentioned in the introduction, were evident in the study results. The ability of TA to reduce oxidative stress and modulate the inflammatory response aligns with these mechanisms.

Histopathological evaluation revealed that tissue damage was significantly greater in the IR group than in the sham group, and this damage was reduced with TA administration in the TA group, although the reduction was not statistically significant. Specifically, the IR group exhibited widespread leukocyte infiltration, significant degeneration of alveolar structures, interalveolar hemorrhage, and thrombosis in the arterioles. These findings are indicative of severe reperfusion injury in the lung tissue. In contrast, the TA group showed a reduction in leukocyte infiltration, alveolar damage, and thrombus formation compared to the IR group, suggesting that TA helps mitigate some aspects of reperfusion injury. However, widespread interstitial edema was still present in the TA group, indicating that TA did not completely prevent all histopathological changes associated with reperfusion injury.

In a study by Sirmali et al.,[23] using ascorbic acid in an experimental lower extremity IR model, polymorphonuclear leukocytes, edema, and congestion were observed in the lung tissue of the IR group, similar to the changes observed in our IR group. Our findings also align with those of Tekinbas et al.,[16] who reported that free radical production during one-lung ventilation caused significant lung injury, as evidenced by intra-alveolar edema, inflammatory cell infiltration, focal hemorrhage, and alveolar destruction.

The tissue MPO and MDA levels indicate local inflammation and oxidative stress, respectively. In our study, while MDA levels were significantly higher in the IR group than in the sham group and significantly lower in the TA group than in the IR group, MPO levels were not significantly lower in the TA group than in the IR group. This finding suggests that TA effectively reduces oxidative stress but may not significantly impact leukocyte activity, as measured by MPO. Pesei et al.[24] also reported increased tissue MPO levels as an indirect indicator of leukocyte activity in lung injury associated with pancreatitis.

In our study, the plasma levels of MPO and MDA were significantly greater in the IR group than in the sham group, indicating an increased systemic inflammatory response and oxidative stress. However, the lack of statistically significant increases in the TA group suggested that while TA did not sufficiently suppress this response, it did reduce oxidative stress. This finding is consistent with studies in the literature, indicating that TA reduces oxidative stress and modulates the inflammatory response. For instance, in a study by Şirin et al.,[25] no pathological findings were observed in the lung histology of rabbits given aprotinin in a lower extremity IR model, and it was concluded that the drug reduced reperfusion injury. Similarly, Köksal et al.[26] demonstrated that aprotinin reduced reperfusion injury more effectively than alpha-tocopherol in a rat IR model.

The serum IMA level is an indicator of oxidative stress following ischemia. In our study, serum IMA levels were significantly higher in the IR group than in the sham group, while they were significantly lower in the TA group than in the IR group. This finding indicates that TA significantly reduces oxidative stress. Turedi et al.[27] also reported increased serum IMA and MDA levels in patients who underwent cardiopulmonary resuscitation due to cardiac arrest in the emergency department, with an increase in serum IMA levels associated with early prognosis after cardiopulmonary resuscitation.

This study has some limitations. Firstly, the use of a single dose of tranexamic acid may not fully capture the dose-dependent effects of the drug. Additionally, the use of heparin may have influenced the antifibrinolytic effects of tranexamic acid, potentially confounding the results. The study focused on short-term outcomes without evaluating long-term effects. Finally, the small sample size for histopathological and biochemical analyses may have limited the statistical power to detect differences between groups.

In conclusion, TA may be useful for reducing inflammatory reactions and oxidative stress in IR injury. The significant results included a reduction in the serum IMA and MDA levels, indicating decreased oxidative stress. Although not all inflammatory markers showed significant decreases, the overall trend suggests potential benefits of TA in reducing inflammatory reactions. Further research is necessary to explore the effects of different doses and long-term effects of TA in various IR models. This study continues the limited number of reperfusion studies involving the TA in the literature, and our findings share common aspects with the results in the literature. More studies are needed to investigate the effects of different doses and long-term effects of TA. This study suggested that TA may be a potential therapeutic option for reducing reperfusion injury, particularly through its local anti-inflammatory effects and its role in reducing oxidative stress.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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