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Effect of Triazolopyridine (Trapidil) on Experimental Hepatorenal Toxicity Induced by Renal Ischemia Reperfusion Injury in Rats

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Abstract

Background: Renal ischemia, followed by reperfusion (I/R) is one of the major causes of Acute Renal Failure (ARF) furthermore it resulted in distant organ dysfunctions. The pathogenesis of I/R is multifactorial.

This study was designed to study the effect of trapidil treatment before renal I/R on hepatic and renal function,

Material and Method: 30 male Sprague-Dawley rats were submitted to right nephrectomy and divided into three groups: Control group, renal I/R group, renal I/R group received trapidil 14mg/kg 7 days before I/R, 24 hours after reperfusion blood samples were collected for evaluation of: Serum Aspartate Aminotransferase (AST), serum alanine aminotransferase (ALT), blood urea nitrogen, serum creatinine, serum Nitric Oxide (NO), Tumor Necrosis Factor-a (TNF-a), Total Antioxidant Capacity (TAC), and serum Monocyte Chemoattractant Protein-1 (MCP-1). All animals were scarified, the liver and left kidney were removed to measure renal and hepatic Malondidhyde (MDA), Glutathione Peroxidase (GPx) and Myeloperoxidase (MPO), histopathological examination for the left kidneys was performed.

Results: Treatment with trapidil (14mg/kg) for 7 days before renal I/R improved renal and hepatic dysfunction as evidenced by significant decrease in blood urea, serum creatinine, and significant decrease in the activity of AST, ALT as compared to renal I/R group in addition trapidil supplementation resulted in significant decrease in serum, TNF-a, MCP-1 as compared to renal I/R group on the other hand it resulted in significant increase in serum NO and total antioxidant capacity in addition it resulted in significant decrease in the level of renal and hepatic tissue MPO and MDA with significant increase in tissue GPx as compared to renal I/R group these results are confirmed by histopathological findings.

Conclusion: Trapidil supplementation before renal I/R can protect the kidney and liver and prevent its damage by increasing NO production with improvement of blood flow, anti-inflammatory and antioxidant effect.

Key Words: *Trapidil – Renal ischemia reperfusion – NO – Hepatorenal dysfunction.*

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Introduction

RENAL I/R injury is one of the major pathophysiologic complications that occurs in cases of heminephrectomy, renal transplantation, cardiac arrest with recovery and vascular surgery. It represents a widespread reason of acute renal failure and renal graft rejection [1]. Several mechanisms have been postulated to explain damage to kidneys due to I/R, these mechanisms involving anoxia, release of oxygen-derived free radicals, neutrophil accumulation, inflammatory responses, modification in NO production and change in TXA2/PGI2 production with change in renal blood flow [2]. Previous studies reported that renal I/R injury may lead to remote organs dysfunction in adding to local renal damage [3]. Liver represents one of organs which may be susceptible to these dysfunctions [4].Increased generation of inflammatory cytokines following renal I/R may induce hepatic tissue damage in association with stimulation of reactive oxygen species and nitrogen species which contribute to pathophysiology of hepatorenal damage [5].

Trapidil (5-methyl-7-diethylamino-s-triazolopyrimidine) is a phosphodiesterase inhibitor and acts as platelet-derived growth factor inhibitor that prevents platelet aggregation; induces synthesis of prostacyclin; decreases lipid peroxidation [6] and it has anti-inflammatory effect by inhibiting the CD40/CD40L pathway of monocytes and macrophages [7]. Trapidil has a vasodilator effect as it acts by increasing the ratio of PGI2/TXA2 where it increase vasodilatory PGI2 and inhibit production of thromboxane A2 [8].

Material and Methods

Thirty male Wistar Albino rats (250-290g); purchased from the Faculty of Science, Tanta

University, were used for this study. The rats were accommodated in a temperature controlled room and on a 12-h light/dark cycle. The rats were fed a normal Purina rat chow diet and let water ad libitum. This work has been done at Physiology Department and all protocols were granted by Tanta Faculty of medicine ethical Committee (2017). After two weeks of acclimatization they were classified into three groups, ten rats each.

Sham operated (Group I). The rats of this group submitted to the right-sided nephrectomy and the left renal artery was dissected and manipulated but no clip applied, and it is considered as control group [9].

Ischemia/Reperfusion (I/R) (Group II). This group were administered distilled water (5ml/kg/ day) orally daily for 7 days before the operation. Renal I/R was carried out as described by (Basiredy et al., 2006) [9] animals anaesthetized with xylazine (10mg/kg, i.p.) and ketamine (75mg/kg, i.p.) purchased from Sigma-Aldrich Co. (Egypt). Through flank incisions, a right-sided nephrectomy was performed then the left renal artery was clamped for 45min by a non-traumatic microvascular clip, then the clamp was removed following the ischemic period for 60 minutes to re-establish blood flow to the ischemic kidney (reperfusion).

I/R trapidil treated (Group III). This group were received trapidil 14mg/kg orally seven days before the operation [10]. Trapidil was purchased from Sigma-Aldrich Co. (Egypt). Ischemia induced by clamping of left renal artery (45min) the clamp has been removed to establish blood flow for 60 minutes (reperfusion period). 24 hours after reperfusion, blood samples were collected in a dry centrifuge tube for serum separation, centrifuged at 3000xg for 15min (4ºC) and stored at 20ºC as aliquots for further determinations of blood urea nitrogen (mg/dl) [11], serum creatinine (mg/dl) [12], serum AST (U/ml) and serum (ALT(U/ml) the levels were measured using commercially available assay kits using standard diagnostic kits (Quimica Clinica Aplicada s.a., Amposta, Spain). Tumor necrosis factor-a (TNF-ct) was quantified with the use of specific Enzyme Linked Immunosorbent Assay (ELISA) kits according to the method of (Carrizo et al., 2007) [13]. Total antioxidant capacity in serum mM/l was measured per method described by Koracevic [14], serum Nitric Oxide (NO) [15] was measured as nitrite reductase method using total Nitric Oxide Kit (Beyotime, Haimen, China, S0023). Serum monocyte chemoattractant protein-1 (MCP-1) was determined by solid-phase ELISA using rat MCP-1 kits (Ono et al.) [16].

24 hours after reperfusion, liver and left kidney were rapidly removed, washed from blood by ice-cold isotonic saline and each divided into 2 parts. The first part of each harvested kidney and liver were shock-freeze in liquid nitrogen (–80ºC) and stored at 20ºC for further determination susceptibility for lipid peroxidation product Malondidhyde (MDA), tissue Glutathione Peroxidase (GPx) and Myeloperoxidase (MPO).

Determination of hepatic and renal MDA level; tissue samples were homogenized with ice-cold 150mM KCl for the determination of MDA level. MDA level was assayed for products of lipid peroxidation by monitoring thiobarbituric acid-reactive substance formation. Results were expressed as nmol MDA/g tissue [17].

Renal MPO activity was measured in tissues in a procedure like that documented by Hillegas et al. [18], while hepatic MPO were determined by double antibody sandwich technique (frank et al.;) [19]. MPO activity was expressed as U/g tissue. The activity of (GPx) were determined according to the method of Luoping Zhang, et al. [20]. The other part of the left kidney together with the liver of each animal were stored in 10% formalin-saline at 4ºC, and then processed for histopathological investigation.

The activities of Glutathione Peroxidase (GPX), SOD and catalase were determined according to the methods of Wheeler et al., [22].

Statistical analysis:

The data was collected and submitted to the personal computer. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS/Version 21) software. Arthematic mean, standard deviation, for categorized parameters, chai square test was used while for numerical data *t*-test was used to compare two groups while for more than two groups ANOVA test was used, flowed by Duncan's method was used to find the significant between each two groups as follows: The difference letters indicate that there was a significant difference between this two groups. *p*-value <0.0 was considered significant.

Results

Table (1), Fig. (1) reveal that renal I/R result in significant increase in the level of serum creatinine, blood urea nitrogen, serum TNF-a, MCP-1also the activity of AST, and ALT were signicantly

increased, while there is significant decrease in serum NO, total antioxidant capacity.

Treatment with trapidil (14mg/kg) for 7 days before renal I/R improves renal and hepatic dysfunction as evidenced by significant decrease in blood urea, serum creatinine, and significant decrease in the activity of AST, ALT as compared to renal I/R group in addition trapidil supplementation results in significant decrease in serum TNF- α, MCP-1 as compared to renal I/R group on the other hand it results in significant increase in serum NO and total antioxidant capacity.

Table (2), Fig. (2) represent that renal I/R results in significant increase in the level of renal and hepatic tissue MPO and MDA with significant decrease in tissue Glutathione Peroxidase (GPx) as compared to control group.

Treatment with trapidil (14mg/kg) for 7 days before renal I/R results in significant decrease in the level of renal and hepatic tissue MPO and MDA with significant increase in tissue glutathione peroxidase GPx as compared to renal I/R group.

Histopathological examination:

The histopathological findings of this study revealed the following:

In control group of this study, it was found that all animals showed normal liver with normal hepatocytes, sinusoids and portal triad as shown in Fig. (3A), also the kidney shows normal glomeruli, tubules and interstitial tissues as shown in Fig. (4A).

In renal I/R group of this study, it was found that the liver of these animals showed diffuse vacular degeneration with focal mononuclear inflammatory cell infiltration as shown in Fig. (3B), also the kidney shows signs of degeneration glomeruli as shown in Fig. (4B).

In trapidil treatment group 7 days before I/R, it was found that trapidil has a protective effect on renal and hepatic tissue where histopathological findings reveal normal hepatocytes with slightly dilated central vein and blood sinusoids in Fig. (3C) and mild tubular damage with normal glomeruli in Fig. (4C).

Table (1): Comparison between control group (Group I), renal I/R group (Group II) and trapidil treated group (Group III) regarding, AST, ALT, Blood urea nitrogen, Serum creatinine, Total Antioxidant Capacity (TAC) and serum NO, TNF α, and MCP-1.

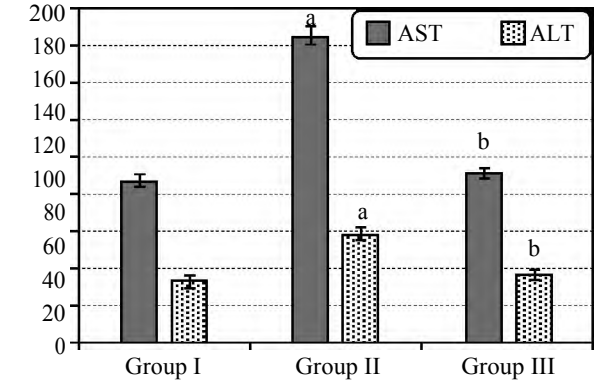
	Group I	Group II	Group III
AST u/ml	96.2±4.01	183.7±5.76**a**	100.93±2.39**b**
ALT u/ml	37.1±2.97	64.9±4.28**a**	39.97±2.96**b**
Blood urea nitrogen mg/dl	35.2±3.30	66.8±4.63**a**	39.1±2.45**b**
Serum creatinine mg/dl	0.46±0.04	0. 84±0.03**a**	0.49±0.02**b**
Total Antioxidant Capacity (TAC) mM/L	1.28±0.08	0.50±0.05**a**	1.22±0.04**b**
Serum NO umol/L	25.4±2.8	11.4±1.9**a**	23.2±1.8**b**
TNFα in serum ng/L	8.1±0.90	36.3±1.90**a**	9.1±0.80**b**
MCP-1 pg/ml	43.4±3.41	184.2±5.37**a**	47.9±3.96**b**

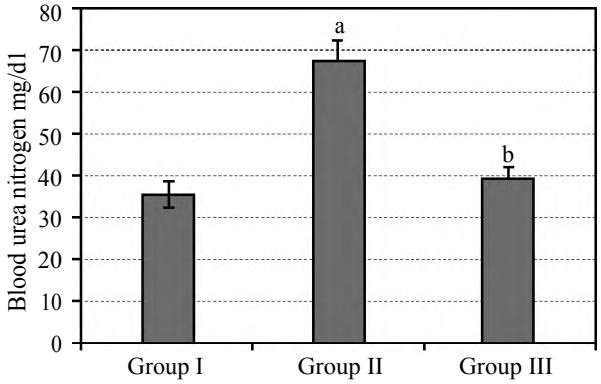
a: Denotes statistical significance with Group I.
b: Denotes statistical significance with Group II.
p-value is <0.05.

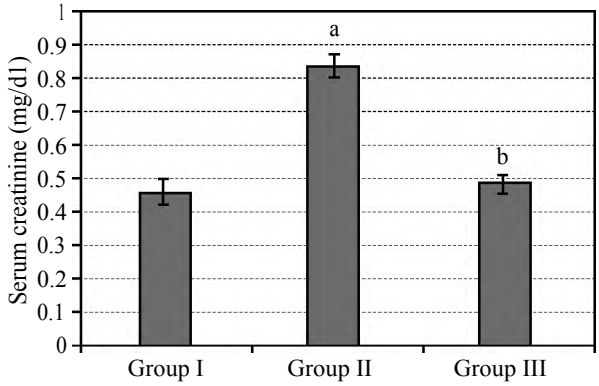
Table (2): Comparison between control group (Group I), renal I/R group (Group II) and trapidil treated group (Group III) regarding renal (GPx), MDA and (MPO) and hepatic (GPx), (MDA) and (MPO).

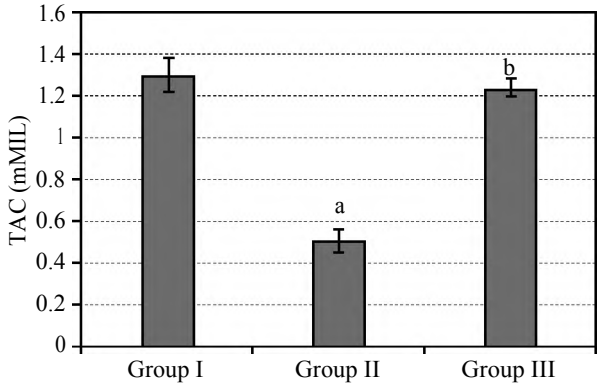
	Group I	Group II	Group III
Liver GPx [illegible]mol/gm tissue protein	0.37±0.03	0.18±0.02**a**	0.34±0.03**b**
Kidney GPx [illegible]mol/gm tissue protein	0.53±0.03	0.15±0.03**a**	0.50±0.02**b**
Liver MDA nmol/gm tissue protein	10.75±0.94	27.40±0.78**a**	11.63±0.73**b**
Renal MDA nmol/gm tissue	4.82±0.27	9.48±0.57**a**	5.21±0.34**b**
Liver MPO u/gm tissue protein	37.01±3.06	75.98±6.12**a**	34.55±1.59**b**
Renal MPO u/gm tissue protein	9.14±1.66	18.61±3.83**a**	11.07±0.96**b**

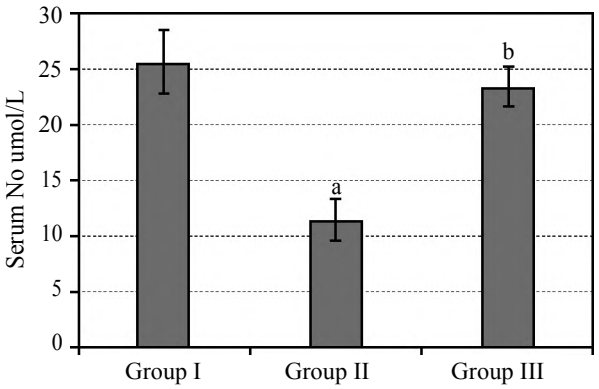
a: Denotes statistical significance with Group I.
b: Denotes statistical significance with Group II.
p-value is <0.05.

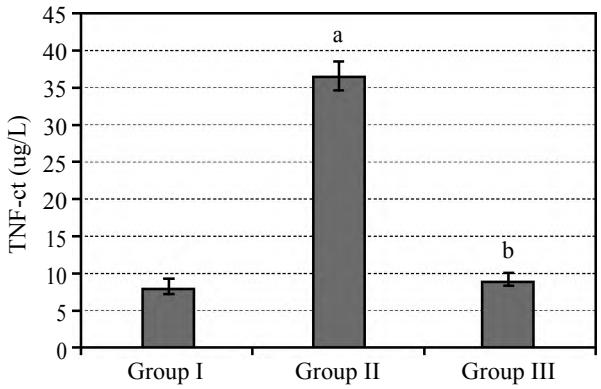












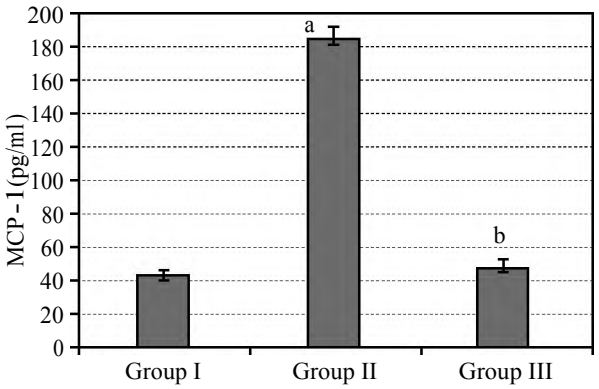


Fig. (1): Comparison between control group (Group I), renal I/R group (Group II) and trapidil treated group (Group III) regarding, AST, ALT, blood urea nitrogen, serum creatinine,Total Antioxidant Capacity (TAC) and serum NO, TNF0C, and MCP-1.

a: Denotes statistical significance with Group I.
b: Denotes statistical significance with Group II.
p-value is <0.05.

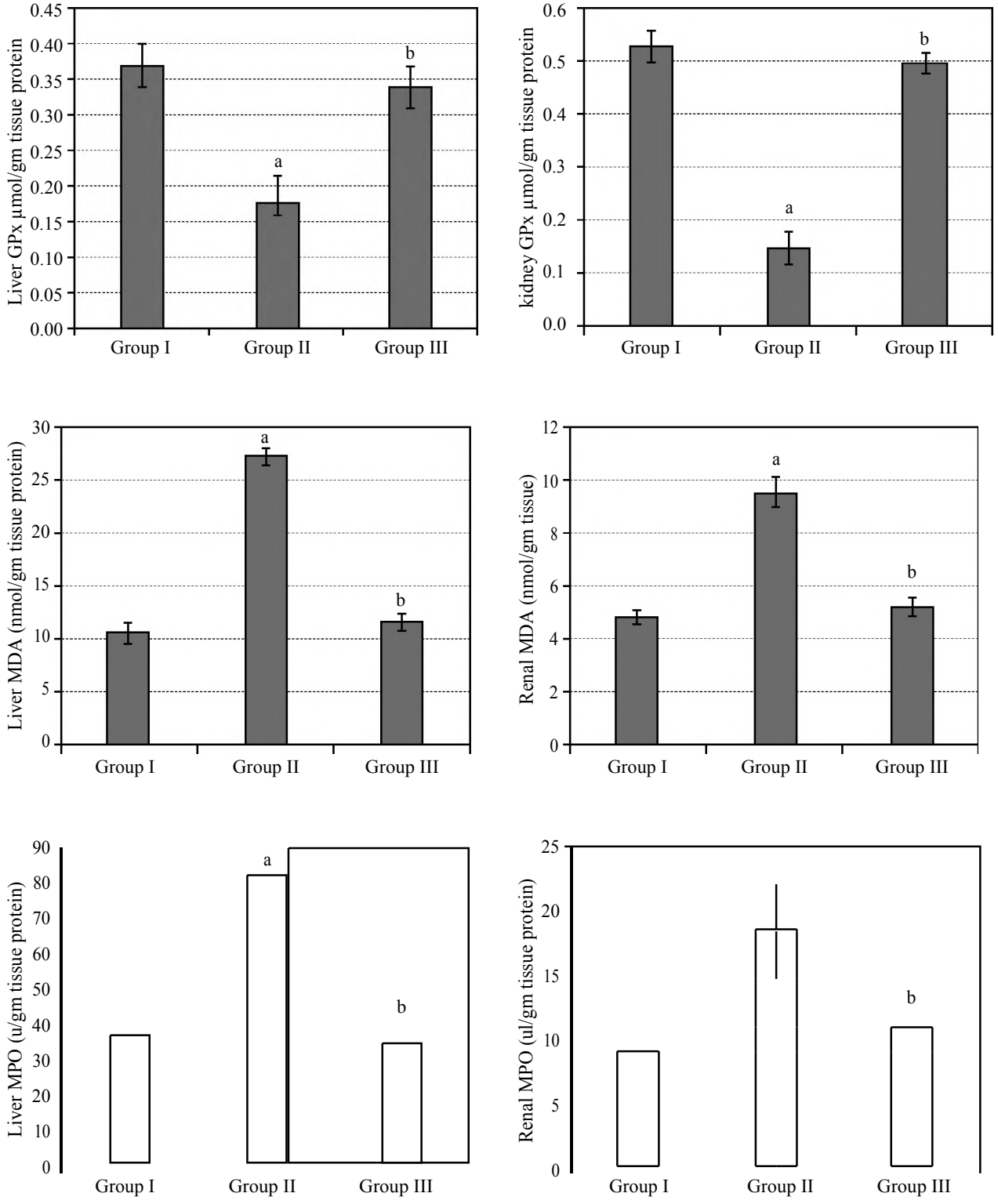


Fig. (2): Comparison between control group (Group I), renal I/R group (Group II) and trapidil treated group (Group III) regarding renal (GPx), MDA and (MPO) and hepatic (GPx), (MDA) and (MPO).

a: Denotes statistical significance with Group I.
b: Denotes statistical significance with Group II.
p-value is <0.05.

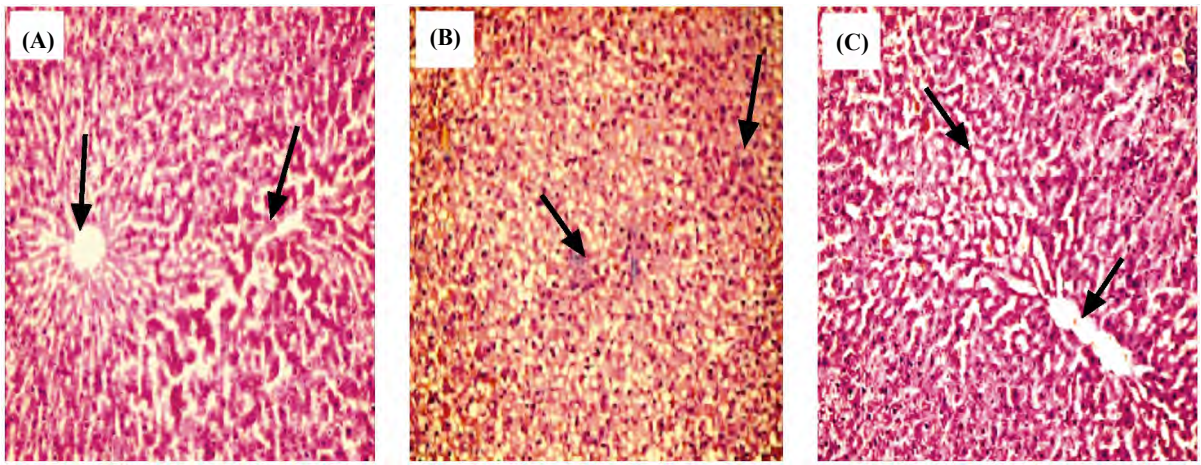


Fig. (3): (A) Liver section showed normal hepatocytes, liver sinusoids and normal portal triad (Group I). (B) Liver section showing diffuse vascular degeneration with focal mononuclear inflammatory cell infiltration (Group II). (C) Liver section showing normal hepatocytes with slightly dilated central vein and blood sinusoids (Group III). Magification H & E X200.

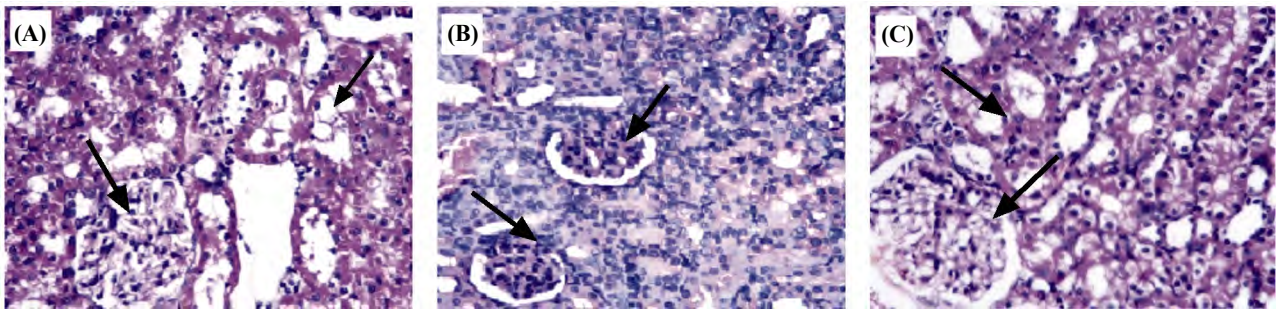


Fig. (4): (A) Kidney section shows normal renal glomeruli, tubules and interstitium (Group I). (B) Renal section shows degenerated renal glomeruli (Group II). (C) Renal section shows Mild tubular damage with normal glomeruli (Group III). Magnification H & E X200.

Discussion

Renal Ischemia Reperfusion (I/R) injury remains one of the biggest problems in the subject of renal transplantation causing acute renal failure [21]. Tissue ischemia with inadequate oxygen supply followed by successful reperfusion initiates a wide and complex collection of inflammatory responses that may both exaggerates local injury as well as induces damage of distant organ function [22,23].

Our study revealed that renal I/R impairs hepatorenal function as demonstrated by significant increase in the level of serum creatinine, blood urea, serum AST and ALT as compared to control group this finding is confirmed by histopathological finding which reveals diffuse vascular degeneration with focal mononuclear inflammatory cell infiltration in the hepatic tissue and degenerated renal glomeruli in kidney tissue our results agree with previous work [24-26].

Induction of hepatorenal toxicity by I/R may be attributed to vascular impairments with increased vascular permeability and endothelial cell inflammation [27,28]. In addition, I/R promotes vasoconstriction by inducing the endothelial productions of vasoconstrictor substances due to change in TXA2/PGI2production with change in real blood flow that worsen vascular damage and induce hepatorenal dysfunction [28,29]. Also significant impairment in hepatorenal function in our study may attributed to endothelial dysfunction and oxidative stress with increased construction of oxygen free radical and consumption of antioxidant enzymes [29]. As evidenced by reduction of total antioxidant capacity, hepatic and renal GPx and significant increase in tissue MDA, furthermore this oxidant stress leads to activation of the NFκB transcription factor, that increases proinflammatory cytokines formation including TNF-a, MCP-1 [30]. This is with accord with our results which reveals significant increase in TNF-a, MCP-1 in I/R group as contrasted to control group. These inflammatory cytokines itself are stimulator for more generation of oxygen free radicals and infiltration of leucocytes and monocyte attraction furthermore neutrophil stick to endothelial cells result in more production

of ROS, proteases and proinflammatory cytokines **[31]** and this explain significant increase in hepatic and renal MPO in our work. Another explanation to I/R hepatorenatoxicity is change in nitric oxide (NO) signaling pathway **[32]** Ghasemi et al., revealed that I/R inhibit the action of a specific NO Synthase (NOS) isoform, for example eNOS, leading to vasodilatation impairments. This upregulation of eNOS has been attributed to increase the synthesis of reactive oxygen species **[33]**. Also, it was proved that the synthesis of NO synthetase enzyme is reduced during ischemia period **[34]**. This is with according of our results which reveal significant reduction in serum NO in I/R group.

Trapidil has a wide spectrum of biological functions. The role of trapidil on various tissue injury has been previously demonstrated **[35]**. Our study revealed that treatment of rats with trapidil 7 days before renal I/R results in improvement of renal and hepatic function as demonstrated by significant decrease in blood urea, serum creatinine, and significant reduction in the activity of AST, ALT as compared to I/R group and this results was confirmed by histopathological finding, this protective effect of trapidil may be attributed to its vasodilator effect with upgrading in renal and hepatic blood flow, where it decreases TXA_2 production and it has antiplatelet and antithrombotic effects it also causes a secondary increase in prostacyclin (PGI_2) production, in addition to an inhibition of TXA_2 synthesis. Increased PGI_2 causes a vasodilatation effect and increases hepatic and renal blood flow **[36]**. Furthermore, inhibition of TXA2 and increase PGI2 may is known to collaborate with the system consisting of eNOS/NO **[37]** with increased NO production, which is in accordance with previous work **[38]** and evidenced by our work where there is significant increase in serum NO after trapidil treatment as compared to renal I/R group. Increased NO production aggravates the vasodilator effect of trapidil and results in recovery in renal and hepatic function. In addition, the phosphodiesterase inhibiting effect of trapidil and its potent role in inhibition of TXA2 which has a role in activation of phospholipase, lipid peroxidation and release of free radical **[39]** explains its antioxidant effect and this is proved in our results by significant decrease in MDA production which is product for lipid peroxidation and indicator for release of free radicals and significant increase in GPx formation and significant increase in total antioxidant capacity in trapidil treated group as compared to renal I/R group.

Trapidil is known to have potent ant- inflammatory effect where it inhibits production of proinflammatory cytokines because of inhibition of CD40 production in monocyte **[40]**. Furthermore, it was proved that is trapidil inhibits leucocyte infiltration **[41]** and this proved by our results by significant decrease in tissue MPO in trapidil treated group as compared to I/R group also there is significant decrease in serum TNF- a, MCP-1 in trapidil treated group as compared to renal I/R group. Trapidil effect on MCP-1 expression may be attributed to its inhibitory effect on PDGF receptor, inhibition protein kinase A, and change in prostaglandin production **[42]**. Reduction in inflammatory cytokines may reduce tissue injury in hepatic and renal tissues and improves its function and inhibits more release of ROS **[43]** these results are supported by histopathological finding in our findings which reveals normal hepatocytes with slightly dilated central vein and blood sinusoids and normal renal glomeruli in group pretreated with trapidil before renal I/R.

Conclusion:

Trapidil supplementation before renal I/R can protect the kidney and liver and prevent its damage by increasing NO production with improvement of blood flow due to its effect on PGI2, anti-inflammatory and antioxidant effect.

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تآثير الترابيدل على التسمم الكبدى الكلوى المستحدث بنقص التروية وإعادة الإشباع فى الكلى فى الفئران

مقدمة: إن نقص وإعادة التروية بالكلى هى واحدة من الآسباب الرئيسية للفشل الكلوى وعلاوة على ذلك فإنه يؤدى إلى إختلال فى الآجهزة البعيدة عن الكلى وقد وجد آن هذا النقص وآسبابه الباثولوجية متعدد العوامل وغيرمقتصر لذا لقد تم تصميم هذا البحث لدراسة تآثير العلاج الترابيدل قبل حدوث نقص التروية الكلوية على الكلى والكبد.

طريقة البحث: آجرى هذا البحث على ٣٠ من ذكور الفئران تعرضت جميعها إلى إستئصال الكلى اليمنى وقسمت إلى ٣ مجموعات: المجموعة الضابطة، المجموعة التى تعرضت لنقص التروية وإعادة الإشباع، والمجموعة التى تناولت عقار الترابيدل قبل نقص التروية ١٤مجم/كجم ٧ آيام قبل العملية. بعد مرور ٢٤ ساعة تم سحب عينة الدم لتحديد ناقلة امين الاسبرتيه وناقلة امين الالانين فى المصل–واليوريا فى الدم، الكريتيانين فى المصل واكسيد النيتريك فى الدم عامل نخر الورم آلفا وإجمالى القدرة المضادة للآكسدة، والبروتين وحيد المصل . ثم تم تشريح جميع الحيوانات وإزالة الكلى اليسرى والكبد لقياس مالوندهيد الكلى والكبد والجلوتاثيون بيروكسيداز وميلوبيروكسيديز. وتم إجراء فحص لآنسجة الكلى والكبد.

النتائج: قد آظهرت النتائج آن العلاج بالترا بيدل ١٤مجم/كجم لمدة ٧ آيام قبل العملية آدى إلى تحسن فى وظائف الكلى والكبد فى المجموعة الثالثة مقارنة بالمجموعة الثانية. كما آدى إلى إنخفاض فى مستوى عامل نخر الورم آلفا والبروتين وحيد المصل وزيادة القدرة الكلية المضادة للآكسدة وآكسيد النيتريك. كما آدى إلى إنخفاض فى مستوى إنزيم المالوندهيد وميلوبيروكسيديز فى المجموعة الثالثة مقارنة بالمجموعة الثانية.

الإستنتاج: هذه النتائج آظهرت قدرة الترابيدل على تحسن وظائف الكلى والكبد بعد نقص وإعادة التروية بسبب تحسن تدفق الدم وزيادة آكسيد النيتريك وتآثيره كمضاد للإلتهابات ومضاد للآكسدة.