Research Article

Renoprotective effect of inhibiting renin-angiotensin-aldosterone system (RAAS) by captopril versus losartan on drug-induced acute kidney injury (AKI)

Muhammad Zafar^{1*}, Iram Mushtaq², Muhammad Zahid Khan³,
Muhammad Khalil Ahmad Khan⁴ and Asmatullah⁵

1. Post-Graduate Department of Zoology, Government Emerson College, Bosan Road, Multan (MZ)-Pakistan

2. Department of Pathology, University of Veterinary and Animal Sciences, Lahore (IM)-Pakistan

3. House Officer, Medical Unit 04, Bahawal Victoria Hospital and Quid-e-Azam Medical College, Bahawalpur (MZK)-Pakistan

4. Department of Zoology, Government Dial Singh College, Lahore (MKAK)-Pakistan

5. Department of Zoology, University of The Punjab, Quid-e-Azam Campus, Lahore-Pakistan

*Corresponding author's email: m.zafar1214@gmail.com

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Abstract

Acute kidney injury (AKI) is a common health problem especially the drug induced AKI is a side or toxic effect during treatment of different medical disorders. The present study was aimed to investigate the renoprotective effect of inhibiting renin-angiotensin-aldosterone system (RAAS) by captopril versus losartan on drug induced acute kidney injury (AKI). In this study sixty (60) male albino rats divided into six groups (10 rats/group); control, AKI, AKI+captopril, AKI+losartan, captopril and losartan have been used. GFR (glomerular filtration rate) and SBP (systolic blood pressure) have been measured. For measurement of MCP-1 (monocyte chemoattractant protein-1), urea, NGAL (Neutrophil gelatinase – associated lipocalin, ICAM-1 (intercellular adhesion molecule -1), cystatin-C and creatinine serum samples were collected. Kidney tissues for measurement of tissue of KIM-1 (Kidney injury molecule-1), MDA (malondialdehyde) and renal expression of megalin were removed. Both losartan and captopril attenuated drug induced acute kidney injury (AKI) as revealed from the measured tissue parameters and serum. As compared to losartan, captopril was found to be superior on normalizing KIM-1, megalin and ICAM-1 while as compared to captopril, losartan improved more GFR. In AKI, groups treated with captopril and groups treated with losartan showed no significant difference in such type of measured parameters. Both are used for acute kidney injury and losartan slow the rate of progression of the experimental renal disease as compared to captopril in future case.

Keywords: Acute Kidney Injury (AKI); Captopril; Losartan; Glomerular Filtration Rate (GFR); Malondialdehyde (MDA)

Introduction

The kidneys are known as susceptible to toxic damage and ischemic because they receive

22% of the cardiac output. In the kidneys certain medications are concentrated secondary to tubular reabsorption or

secretion which can predispose patients for renal injury. Acute renal failure (ARF) can develop due to pre-renal, post renal or intrinsic renal causes [1].

AKI (Acute Kidney Injury) which is characterized due to rapid loss of the ability of the kidneys to concentrate urine, excrete wastes, maintain fluid balance and conserve electrolytes [2]. The RAAS (Renin Angiotensin Aldosterone System) was considered as an endocrine system with angiotensinogen which is produced by the liver that is cleaved by renin and released from the cells of renal juxtaglomerular. By this way AngI (angiotensin I) is generated which in turn is further cleaved by ACE (Angiotensin Converting Enzyme) activity of the lungs into AngII (Angiotensin II) active form.

Then in the adrenal cortex Ang II binds to specific receptors and resulting in the release of aldosterone. In this way in the collecting duct, the cardinal function of the renin angiotensin aldosterone system (RAAS) is maintaining of blood pressure due to Ang II-induced aldosterone – mediated sodium retention and vasoconstriction [3].

Local the renin angiotensin aldosterone system (RAAS) has been described to operate independently due to their systemic counterpart. In the proximal tubular cells of the kidney a local RAAS including all of its components could have been shown. Proximal tubular cells actively secrete angiotensinogen into the urine and also produce Angiotensin II (Ang II). In the distal tubule, intraluminal angiotensinogen may be converted into Angiotensin II (Ang II) and observations suggest that it leads towards the induction of sodium channels which are independent of aldosterone. Directly or indirectly, renal injury activates the local renin angiotensin aldosterone system (RAAS) [4].

The present study was aimed to evaluate and compare the renoprotective effects of

inhibiting renin angiotensin aldosterone system (RAAS) by losartan versus captopril on AKI (Acute Kidney Injury).

Materials and methods

Design study

Sixty (60) male albino rats of four (4) months old weighing 130-160gms constituted the animal model in this study. Rats were housed five (5) per cage with room temperature $25\pm 2^{\circ}\text{C}$. These rats were kept under the standard protocol of 12 hour day and night (light/dark) cycles, in 14"X20" steel cages and had free access to water and food. The rats were fed upon commercially prepared chick feed pellets (Chick Feed No.3, Punjab Poultry Feed Pvt. Limited). This feed was further enriched with vitamins (Optilets-M, Abbott Laboratories (Pakistan) Limited) before it was supplied to the animals. Followed ethical recommendations which had been approved by the local scientific and ethical committee, the animals were handled and experimental steps and scarification were done.

Experimental groups / procedure

All animals were divided into six (6) groups (10 rats / group).

1. Group 1 was known as control group which received saline water through intraperitoneal (i.p) injection for 15 days.
2. Group II was known as Gentamicin group (also known as Acute Renal Failure (ARF) group) which received gentamicin (garamicin, 80mg Sandoz GMP, Switzerland) through intraperitoneal (i.p) injection as 100mg/kg/day for 15 days [5].
3. Group III was known as losartan group which received per oral by oral gavage (losartan, Hikma Pharmaceutical PLC, Jordan) as 10mg/kg/day for 15 days [5].
4. Group IV was known as Acute Renal Failure (ARF) and losartan group (ARF+losartan) which received injection of 100mg/kg/day gentamicin and oral losartan of 10mg/kg/day for 15 days [5].

5. Group V was known as captopril group which received captopril as 10mg/kg/day per oral by oral gavage (Capoten, 25mg, Pharmadex, American) for 15 days [6].

6. Group VI was known as Acute Renal Failure (ARF) and captopril group which receive injection of gentamicin 100mg/kg/day and oral captopril of 10mg/kg/day for 15 days [6].

At the end of the study all experimental animals were weighted. These experimental male albino rats were placed in steel cages for the period of 24 hours urine collection. Volume of the urine was also measured and then centrifuged for the separation of debris. At -80°C the urine samples were kept until further analysis.

Determination of Glomerular Filtration Rate (GFR)

After collection of urine for the period of 24 hours and taking the body weight glomerular filtration rate (GFR) was calculated with the help of the following formula [7].

$$\text{GFR (ml/min/kg)} = \frac{\text{urinary creatinine (mg/dl)} \times \text{urine volume (ml)} \times 1000 \text{ (gm)}}{\text{plasma creatinine (mg/dl)} \times \text{body weight (gm)} \times 1440 \text{ (min)}}$$

In the studied groups systolic blood pressure was measured. Then by either inhalation all these albino rats were anesthetized and for the measurement of cystatin C, serum urea, Monocyte Chemoattractant Protein-I (MCP-I), Neutrophil gelatinase-associated lipocalin (NGAL), Inter cellular Adhesion Molecule I (ICAM-I) and creatinine the blood is withdrawn from retroorbital venous sinuses. For the measurement of tissue MDA (Malondialdehyde), KIMI (Kidney Injury Molecule) and renal expression of Megalin, Animals were sacrificed and kidneys were removed.

Measurement of Arterial Systolic Blood Pressure (ASBP)

At 30°C in the tail cuff method, the animals were warmed for 35 minutes in a

thermostatically controlled heating cabinet (Ugo Basille, Italy). For better experimental detection of pulse of tail artery, the tail was passed with the help of a miniaturized cuff and a sensor of a tail-cuff that was attached to an amplifier (ML 130 NIBP, AD Instruments, Australia) [8].

In albino male rats for the measurement of systolic blood pressure (SBP) the tail cuff is known as a common and convenient non-invasion method. Through this the tail cuff first of all is inflated and then deflated. When the cuff is inflated pulsations will be disappear and when the cuff is deflated pulsations will start appearing and then the pressure in the cuff will be equal to the systolic pressure. So the cuff will be attached to a tail cuff sphygmomanometer and blood pressure (BP) will be recorded on a chart [9]. With the help of a non-invasive blood pressure (BP) monitor (model ML 130 NIBP, AD Instruments Pty. Ltd., Sydney, Australia) systolic blood pressure (SBP) and heart rate of animals were indirectly measured each week from the tail of conscious rats through the tail-cuff method for which all animals were pre-trained until blood pressure (BP) was steadily recorded with restrained and minimal stress. By the method described by [8] training was conducted. Cuff deflation pressure (Systolic Blood Pressure (SBP)) was defined as the point through which the cuff pressure is corresponded to the restoration of the first pulse of caudal artery. On each occasion the average of at least three readings (measurements) was taken. By a counter triggered through the pulse wave heart rate was automatically recorded.

Biochemical Measurements/Real-Time RT-PCR (Reversal Transcriptase Polymerase Chain Reaction)

Using the SV Total RNA Isolation Kit (Promega, Madison WI) total RNA was isolated from kidney tissue through the manufacturer's instructions including a treatment step of DNAase. According to

manufacturer's protocol by using the Superscript II Reverse Transcriptase Kit (Invitrogen) / μg of RNA was then reverse transcribed into complementary DNA (cDNA). By using emission from SYBR Green (SYBR Green Master Mix, Applied Biosystems), amplification and detection were performed in an optical 98-well plate with an ABI PRISM 7600 fast sequence detection system (Applied Biosystems, Carlsbad, California). PCR cycles which were consisted of 40 cycles at 95°C for 15 minutes and 60°C for 60 seconds after an initial activation step at 50°C for two minutes and a hot start at 95°C for ten minutes. The sequence of Polymerase Chain Reaction (PCR) primer pairs used are shown in Table 1. Data were analyzed through the detection system of ABI Prism Sequence Software quantified by using the version of 1.7 Sequence Detection Software from PE Biosystems (Foster City, CA). By using the comparative threshold cycle method relative expression of studied genes was to be calculated. All values were normalized to the glyceraldehydes-3-phosphate dehydrogenase (GADDH) which was used as the source of the control housekeeping gene [10].

Estimation of Malandialdehyde (MDA)

In kidney tissues, lipid peroxidations were estimated through measurement of TBARS (Thiobarbituric acid reactive substances) with the help of method of [11]. To 0.2ml of the sample, 0.9% TBA and 22% acetic acid were added. Then mixture of pyridine was added and after that the contents were vortexed thoroughly for the period of two minutes. At 3000rpm after centrifugation for the period of ten minutes the upper most layer was taken and its OD was read at 534nm. The lipid peroxides levels were expressed as millimoles of TBARS/mg protein i.e. thiobarbituric acid reactive substances / mg protein.

MCP-I, Serum Cystatin, lipocalin and CAM-A were detected through ELISA kit (supplied by R and D System, USA) according to the instructions by manufacturer.

Serum, serum urea and urine creatinine were measured with the help of colorimetric methods according to the instructions by manufacturer (Bio Assay System, USA).

Statistical analysis

By using the statistical package SPSS version 21 (IBM SPSS Statistics 21, IBP Corporation, New York, USA) data were coded and entered for Microsoft Windows. With the help of means and standard deviation data was summarized. By using ANOVA-1 (Analysis of Variance-1) comparisons between groups were done with multiple comparisons of Post Hoc Bonferroni test. Probability values (P-Values) less than 0.05 were considered to be as statistically insignificant [12].

Results

In AKI group compared to the control group a significant ($P \leq 0.05$) increase of systolic blood pressure was to be found. Similarly administration of either captopril or losartan in AKI (acute kidney injury) groups showed significant ($P \leq 0.05$) decrease of SBP (Systolic Blood Pressure) as compared to that of untreated AKI group. In SBP (Systolic Blood Pressure) in AKI (acute kidney injury) groups which were treated with captopril or losartan showed no significant difference.

In AKI (acute kidney injury) group GFR (glomerular filtration rate) was found to be significantly ($P \leq 0.05$) decreased as compared to the control group. Similarly, captopril or losartan therapy showed significantly ($P \leq 0.05$) increased GFR glomerular filtration rate) as compared to untreated AKI (Acute Kidney Injury) group. Significant ($P \leq 0.05$) increase of GFR (glomerular filtration rate) showed by losartan as compared to AKI (acute kidney injury) group which was treated with captopril.

Table 1. Primer Sequences used for Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)

Primer	Sequence
KIM-I	Forward Primer 5' - AGAGAGAGCAGGACACAGGCTT - 3' Reverse Primer 5' - ACCCGTGTAGTCCCAAACA - 3'
GAPDH	Forward Primer 5' - GATGCTGGTGCTGAGTATGTCG - 3' Reverse Primer 5' - GTGGTGCAGGATGCATTGCTCTGA - 3'
Megalin	Forward Primer 5' - GATGCTGTTGCTGGCGATCG - 3' Reverse Primer 5' - GCATTGTCACAGCGAAAATTCCCAC - 3'

In AKI (Acute Kidney Injury) group as compared to the control group a significant ($P \leq 0.05$) increase of serum urea, cystatin, NGAL, MCP-1, creatinine and ICAM-1 in AKI (Acute Kidney Injury) group was to be found. Captopril or losartan therap in AKI (Acute Kidney Injury) group showed a significant ($P \leq 0.05$) decrease of serum urea, MCP-1, NGAL, ICAM-1, cystatin and creatinine compared to AKI (Acute Kidney Injury) group. Similarly, no significant difference was to be found in most of the measured serum parameters in protective effect offered by captopril versus losartan except for ICAM-1 which showed significant ($P \leq 0.05$) decrease in AKI (Acute Kidney Injury) group treated with losartan to AKI (Acute Kidney Injury) group treated with captopril (Table 2).

Significant ($P \leq 0.05$) increase of renal expression of KIM-1 and MDA was showed by AKI (Acute Kidney Injury) group as compared to that of control group. Administration of captopril or losartin with AKI (Acute Kidney Injury) group showed a significant ($P \leq 0.05$) decrease of KIM-1 and

MDA expression as compared to that of AKI (Acute Kidney Injury) group. No significant difference was to be found in MDA expression in AKI (Acute Kidney Injury) groups with losartan versus AKI (Acute Kidney Injury) group which received captopril, however, significant ($P \leq 0.05$) reduction showed by KIM-1 expression in AKI (Acute Kidney Injury) group to which was treated with captopril as compared to AKI (Acute Kidney Injury) group which received losartan (Table 3).

In AKI (Acute Kidney Injury) group as compared to control group megalin expression was found to be significantly ($P \leq 0.05$) decreased. Administration of captopril or losartan to AKI (Acute Kidney Injury) groups showed a significant ($P \leq 0.05$) increase of megalin expression as compared to that of untreated AKI (Acute Kidney Injury) group. In AKI (Acute Kidney Injury) group, captopril treatment showed a significant ($P \leq 0.05$) increase of megalin expression as compared to that of AKI (Acute Kidney Injury) group treated with that of losartan (Table 3).

Table 2. Studied Groups shown by Biochemical Parameters Measured in Serum.

	Control (n=10rats)	AKI (n=10rats)	AKI +Captopril (n=10rats)	AKI +Losartan (n=10rats)	Losartan (n=10rats)	Captopril (n=10rats)
Urea (mg/dl)	37.70±11.92	90.28±7.86*	55.35±10.06*#	51.33±8.87*#	39.67±4.77#\$	43.27±7.21#\$
Cystatin (mg/dl)	0.76±0.19	3.72±2.48*	2.29±0.58#	2.50±0.47#	0.90±0.31#	0.86±0.22#
Creatinine (mg/dl)	0.15±0.07	1.55±0.58*	0.70±0.25*#	0.69±0.22*#	0.16±0.08#\$	0.16±0.08#\$
NGAL (ng/dl)	152.99±4.6	218.5±12.64*	119.07±30.63#	135.44±32.92#	110.61±8.9	104.18±6.88
ICAM-1 (pg/ml)	139.6±7.73	190.3±17.48*	39.771±7.66*#\$	57.94±8.49*#	37.37±7.08	35.09±6
MCP-1 (pg/ml)	39.17±3.36	107.6±24.08*	50.70±16.25#	59.23±17.99#	36.4±6.776	33.36±4.83

*: statistically significant compared to corresponding values in the control group.

\$. statistically significant compared to corresponding value in AKI (Acute Kidney Injury) + losartan group at $P \leq 0.05$.

#: statistically significant compared to corresponding value in AKI (Acute Kidney Injury) group.

AKI (Acute Kidney Injury)

ICAM-1 = Intercellular Adhesion Molecule 1

MCP = Monocyte Chemo-attractant Protein 1

NGAL = Neutrophil Gelatinase Associated Lipocalin

Table 3. Studied Groups Show Biochemical Parameters measured in Kidney Tissue.

	Control (n=10rats)	AKI (n=10rats)	AKI +Captopril (n=10rats)	AKI +Losartan (n=10rats)	Losartan (n=10rats)	Captopril (n=10rats)
Megalin (Relative Expression)	0.27±0.166	0.160±0.50*	0.99±14*#\$	0.30±0.14#	1.6±0.45	1.42±0.6
KIM (Relative Expression)	8.05±4.2	13.6±1.577*	2.43±1.472*#\$	6.06±2.158*#	1.31±0.428	1.31±0.27
MDA (mmol/mg)	3.1±4.27	8.8±4.67*	2.782±1.24*#	5.6±1.477*#	1.28±0.44848	1.77±0.789

*: statistically significant compared to corresponding values in the control group.

\$. statistically significant compared to corresponding value in ARF (Acute Renal Failure) + losartan group at $P \leq 0.05$.

#: statistically significant compared to corresponding value in ARF (Acute Renal Failure) group.

MDA = Malondialdehyde

AKI = Acute Kidney Injury

KIM-1 = Kidney Injury Molecule -1

Discussion

AKI (Acute Kidney Injury) is known as a common health problem particularly the drug

induced AKA as a toxic or side effect during the treatment of several medical disorders. In different tissues and organs the existence of

independent RAAS (Renin Angiotensin Aldosterone System) has been reported. In the kidney, all components of the renal RAAS (Renin Angiotensin Aldosterone System) which are produced being completely independent of the RAAS (Renin Angiotensin Aldosterone System) and contribute to the progression of both chronic and acute diseases of kidney [13]. In the current study at two different levels we have to evaluate the renoprotective effect of blocking RAAS (Renin Angiotensin Aldosterone System); by AII receptor blocker (ARB) losartan and by ACEI (Angiotensin converting enzyme inhibitor).

The results through this study showed renoprotective effects of both losartan and captopril in AKI (Acute Kidney Injury) which as revealed from their effects on glomerular filtration rate (GFR), blood pressure, tissue parameters and measured serum. Regarding some of the measured biochemical parameters captopril effect was found to be superior as compared to the losartan. However, on glomerular filtration rate (GFR) losartan had a better effect.

According to our results, [14] found that losartan and captopril slow the rate of progression of experimental diseases of kidney.

For the progression of kidney diseases increased AII activity was found to be as a risk factor. Increasing clinical evidence has been found due to the combining of angiotensin converting enzyme inhibitor (ACEI) with AII receptor blocker (ARB) which reduces blood pressure and protein urea in patients captured with renal diseases [15]. For the development of contrast-induced nephrotoxicity, the abnormalities of renal perfusion which are mediated by the RAAS (Renin Angiotensin Aldosterone System) are responsible.

Administration of the ACEI (angiotensin converting enzyme inhibitor), captopril, offers protection against the development of CIN (Contrast Induced Nephrotoxicity) [16].

With response to our results, [17] reported that on endogenous levels of angiotensin losartan has specific tissue effects. Furthermore, [18] in a study reported that losartan decreased blood cystatin C levels and attenuated tubular necrosis, inflammatory cell infiltration and renal fibrosis.

In some study of two years course of antihypertensive therapy with either captopril or losartan showed significantly reduced UAC (Urinary Albumin Creatinine) ratio in the patients of type II diabetic during early nephropathy. With each treatment the reduction in urinary albumin creatinine (UAC) is similarly related to that of acute blood pressure (ABP) [19]. In patients with type II diabetes and nephropathy losartan conferred significant renal benefits and it was generally well tolerable [20].

Cystatin C is known as a 122 amino acid with low molecular weight protein belongs to the member of cysteine proteinase inhibitors [21]. By all nucleated cells it is produced at a constant rate. It is freely filtered through glomerular, reabsorbed and then catabolized while not secreted through the renal tubules [21]. Cystatin C is also known as the most sensitive indicators of nephrotoxicity [22]. Unlike creatinine its serum concentration appears to be the most independent of sex, muscle mass and age [23].

In most nephrons inhibition of the RAAS (Renin Angiotensin Aldosterone System) or AII receptor blocker (ARB) represents to a reversible reduction process in intraglomerular pressure. For the maintenance of renal function the remnant nephrons are present which function at a higher baseline pressure [24].

Monocyte Chemoattractant Protein-1 (MCP-1) belongs to a chemokine family and is known as a potent chemotactic factor for monocytes [25]. MCP-1 was described as an increased expression in experimental and human forms of glomerulonephritis [26]. For mononuclear inflammatory processes the

MCP-1 is known as a biomarker and acts a mediator of acute ischemic (AC) and toxic kidney injury (TKI) [27].

In glomeruli, MCP-1 expression is increased and tubulointerstitial space associated with Angiotensin II (AngII) dependent hypertension [28]. In vitro in vascular smooth muscle cells Angiotensin II has been shown to increase MCP-1 synthesis [29], while in vivo study in experimental models of immune mediated glomerulonephritis blocked of AngII reduced the induction of MCP-1 [30].

For leukocyte adhesion during the process of inflammation, adhesion molecules are required. Leukocyte adhesion leads to the extension and inflammation of cellular injury. In pathophysiology of AKI (Acute Kidney Injury), ICAM-1 (Intercellular Adhesion Molecule-1) plays an important role [31].

Deficiency of ICAM-1 not only decreased neutrophil adhesion against LPS-induced ARF (Acute Renal Failure) but also by abrogating signaling stages that occurred upon ligation of ICAM-1 in endothelium [32].

In concerned with our results, RAAS (Renin Angiotensin Aldosterone System) with valsartan in combination with a statin (fluvastatin) in mouse model of atherosclerosis reduced the level of superoxide anion, atherosclerotic lesions and the expression level of ICAM-1 and MCP-1 (Monocyte Chemoattractant Protein-1) indicating that oxidative stress and blocking inflammation has beneficial effects on endothelium [33]. A reduction on cardiovascular stages showed by clinical studies following blood pressure lowering positively altering vascular wall or endothelium structure which indicates reduction of cardiovascular disease. Vascular function and endothelial activity by increasing number bioavailability improved by several RAAS (Renin Angiotensin Aldosterone System) inhibitors such as ARB (Angiotensin II Receptor Blocker) and ACEI (Angiotensin Converting Enzyme Inhibitor) [34].

NGAL (Neutrophil Gelatinase-Associated Lipocalin) belongs to the lipocalin family is a small 25-K Da protein is a biomarker of tubular damage that secretes tubular protein when entered rapidly both in serum and urine after the onset of AKI (Acute Kidney Injury) [35]. Decreased serum neutrophil gelatinase-associated lipocalin (NGAL) levels in animal models of renal interstitial fibrosis which were treated with ACEI showed [36] in agreement with our study. In patients with diabetic nephropathy which were treated with ARB showed no significant change in urinary neutrophil gelatinase-associated lipocalin (NGAL) by [37].

Malondialdehyde (MDA) is known as a marker of lipid peroxidation. In gentamicin-induced acute renal failure [38] have examined the role of lipid peroxidation in accordance with our findings. Aliskiren on AKI (Acute Kidney Injury) induced by ischemia-reperfusion [39] studied the effect of blocking RAAS (Renin Angiotensin Aldosterone System) by direct renin inhibitor and showed decrease of renal and increased of lipid peroxidation MDA after the administration of aliskiren.

Megalin is known as a single transmembrane receptor protein of 600-K da, belongs to the family of low-density lipoprotein, responsible for the normal tubular reabsorption of all types of filtered proteins that mediates the recovery of important substances which otherwise would be lost in the urine [40]. Megalin in the the kidney is expressed in the proximal part and showed much lower level in glomerular podocytes [41]. In different models of AKI (Acute Kidney Injury) different changes in megalin mRNA expression have been demonstrated. A decrease in renal megalin mRNA expression was to be observed AKI (Acute Kidney Injury) and LPS-induced acute endotoxemia. This type of decrease was found to be associated with that of increased excretion of urinary albumin [42].

Renin is known as a ligand for megalin. In its tubular retrieval, partial megalin deficiency is known as substantial urinary renin excretion which shows the role of megalin [13]. In the transcytosis of RAS components a role for megalin has thus been demonstrated [43]. From the ultrafiltrate process the early proximal tubule shows very effective, megalin-dependent endocytotic uptake and intracellular storage of AGT and renin [44].

Kidney injury molecule-1 (KIM-1) is known as a Type I transmembrane glycoprotein which is localized in chronic and acute injury in the apical membrane of dilated tubules [45]. KIM-1 plays an important role in the processes of regeneration after epithelial injury and through phagocytosis the removal of dead cells in the tubular lumen [46]. In proteinuria a reduction is accompanied through the reduction in urinary KIM-1 (Kidney Injury Molecule-1) excretion with renin-angiotensin-aldosterone blocked [47].

In the kidneys of a wide variety of human diseases and in different animal models, KIM-1 is upregulated. Into the urine, a large quantity of KIM-1 protein is also shed, making it a useful and purposeful urinary biomarker for AKI (Acute Kidney Injury) [46]. KIM-1 also performs as a receptor, scavenger and mediates the uptake of modified necrotic cell debris and low-density lipoprotein [44].

Conclusion

Both losartan and captopril attenuated drug induced AKI (Acute Kidney Injury) as concerned from the tissue parameters and measured serum. Captopril was found to be superior to losartan on normalizing megalin, KIM-1 and ICAM-1, however, losartan has improved GFR (glomerular filtration rate) more as compared to that of captopril, while other parameters in AKI (Acute Kidney Injury) groups which were treated with losartan and groups which were treated with captopril showed no significant difference.

For histopathological evaluation of the renal tissue for further examination of the state of

medulla and the cortex of the kidney we recommend more studies by other blockers of RAAS (Renin Angiotensin Aldosterone System).

Authors' contributions

Conceived and designed the experiments: M Zafar, Performed the Experiment: M Zafar, Analyzed the Data: MKA Khan, I Mushtaq & MZ Khan, Supervised the Experiment: Asmatullah, Contributed reagents/ materials/ analysis tools: M Zafar, MKA Khan, I Mushtaq, MZ Khan & Asmatullah, Wrote the paper: M Zafar.

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