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Protective effect of montelukast against acute kidney injury in rats induced by diclofenac

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Abstract

Background: Acute kidney injury (AKI) is a syndrome encompassing much different etiology and is characterized by an acute deterioration of kidney function. Montelukast is work as an antagonist of the CysLT1 receptor which commonly used in medical treatment of asthma and allergic rhinitis.

Aim: This study was aimed to evaluate the protective effect of montelukast on acute kidney injury in male rats induced by diclofenac.

Materials and Methods: Thirty male rats were divided into five groups: Group1 received no treatment and served as a negative (-ve) control group. Group2 received ethanol and served as (vehicle group). Group3 (disc. Group) administrated diclofenac sodium (vulturine) at a dose (100 mg/kg, i.p.) for three days (20) and served as (diclofenac-treated group). Group 4 (disc. +mont.) received montelukast 30 min. The heart blood samples were taken from the heart; then it centrifuged for five minutes at 3000 rpm to prepare the serum. Creatinine and urea were measured using Chemistry Analyzer, while serum GSH and serum MDA concentrations were measured using ELISA technique. The histopathological changes of the kidney were evaluated by using a routine histopathological technique.

Results: Diclofenac plus montelukast treated group associated with significantly ($p < 0.05$) decreased serum urea and creatinine in comparison with the diclofenac-treated group. The results also revealed that diclofenac-treated group was significantly ($p < 0.05$) decreases serum GSH level when compared with –ve control group. Diclofenac plus montelukast treated group associated with significantly ($p < 0.05$) increased serum GSH level in comparison with the diclofenac-treated group. Diclofenac plus montelukast treated group was associated with significantly ($p < 0.05$) decreased serum MDA level in comparison with diclofenac. The histopathological results showed that montelukast treated group presented with mild Proteinaceous casts accumulation in kidney tubular lumen, mild congestion, and no tubular necrosis.

Conclusion: montelukast has a protective effect against diclofenac-induced acute kidney damage through its effect on kidney biochemical parameters and oxidative stress markers.

Keywords: montelukast; Acute kidney injury; diclofenac.

INTRODUCTION

Acute kidney injury (AKI) is a syndrome encompassing much different etiology and is characterized by an acute deterioration of kidney function [1]. AKI is resulted in decrease the physiological function of kidney and characterized by a reversible increment in nitrogenous waste products, and serum creatinine concentration with a decrease in kidney functions results in electrolyte disorders and decrease urine output [2]. Acute kidney injury recorded in many countries. Moreover, it is associated with increased mortality and morbidity in adults and children.

Moreover, it may be a development the diseases to chronic renal failure [3]. Acute kidney injury is causing deaths in people to reach two million years because the death occurs due to renal failure [4]. Acute necrosis in tubular of the kidney is acute kidney injury that occurs in patients that get in the hospital, and it usually leads to nephrotoxic or ischemic. One of secondary complication is acute interstitial nephritis that may be occurring, such as most common medication misuse [5]. Drugs such as NSAIDs are one of used medications classes in the USA [6]. Despite their several adverse side effects such as renal dysfunction and gastrointestinal bleeding and [7,8].

Diclofenac or called traditionally Voltaren is widely used as anti-inflammatory and analgesic. May studies founded renal dysfunction, or renal failure is detected in who take these drugs. Renal dysfunctions are usually associated with older peoples [9].

Acute renal failure has two form; two forms are occurring due to NSAID administration [10]. In rodents, Diclofenac may cause nephrotoxicity (11) and rising creatinine and urea level in serum that means a clear indicator for nephrotoxicity in rats [12,13]. Free radical (nitric oxide, hydroxyl radical, peroxynitrite, superoxide anion, singlet oxygen, hydrogen peroxide, etc.) are normally formed in the body and its deactivated by specific enzymes such as (catalase, superoxide dismutase and glutathione peroxidase) or by non-enzymatic methods such as (vitamin A, vitamin C and glutathione) [14]. Antioxidants and oxidants are in balance in the body. The oxidative stress is activated when free radicals are formed excessively or/, and the antioxidants are insufficient. However, the oxidative stress results in lipid peroxidation such as Malondialdehyde [15]. Montelukast is work as an antagonist of the CysLT1 receptor which commonly used in medical treatment of asthma and allergic rhinitis [16]. Montelukast has a gastroprotective effect on alendronate induced lesions and indomethacin-induced ulcerations of rat stomach that have a protective effect on oxidative damage activity [17]. Montelukast has ameliorated effect against sepsis and burns [18]. Also, the montelukast have a positive effect on acute lung injury in rats [19]. However, the effect of montelukast on AKI caused by diclofenac will be established in this research.

MATERIALS AND METHODS

Animals

The animals that used in our study are thirty of white male rats weight (200-250g) as average. The animals were housed and placed in auto control air-conditioned room wherever the animals exposed to (12 h light and 12h dark) continually at humidity (60–70%) and temperature (25±2◦C).

Sample collection and experimental design:

The experimental animals were divided into five groups: Group1 received no treatment and served as a negative (-ve) control group. Group2 received ethanol and served as (vehicle group). Group3 (disc. Group) administrated diclofenac sodium (vulturine) at a dose (100 mg/kg, i.p.) for three days (20) and served as (diclofenac-treated group). Group 4 (disc. +mont.) received montelukast 30 min. Before diclofenac administration (20mg p.o). At the end of the experiment (3 days) after (24) h from the last injection, thiopental sodium was used for anesthetizing the animals intraperitoneally at a dose (50 mg/kg). At the trial end, all rats were killed by using thiopental sodium as the dose (100 mg/kg). After opening rat abdominal cavity; Right kidneys were washed with distilled water then keep in formaldehyde (10%) for making histopathological testing. Direct heart puncture collected blood for assessment of serum urea, creatinine, GSH, and MDA concentrations.

The creatinine and urea and estimation

The heart blood samples were taken from the heart; then it centrifuged for five minutes at 3000 rpm to prepare the serum. Creatinine and urea are measured by using Chemistry Analyzer Cobas Mira plus CC (made in Switzerland).

Assay of GSH and MDA levels

Serum GSH concentrations (µg/ml) was assayed by using GSH (Glutathione) ELISA Kit Catalog No: E-EL-0026 (96T) that obtained from Elabscience Biotechnology Inc. while serum MDA concentrations (ng/ml) was assayed by using MDA (Malondialdehyde) ELISA Kit Catalog No: E-EL-0060 (96T) that obtained from Elabscience Biotechnology Inc.

Kidney Histopathological

The kidney preserved in buffered formalin (10%) for (24) hours and washed with ethanol (70%). Then store in a metal container, then it was stirred by a magnetic stirrer, then dehydrated by using differences in series concentration of alcohol from (70-100) %. After that insert in the paraffin. Rotary ultra-microtome uses to cutting paraffin block; the slide prepares after cutting and dried for overnight. The light microscope was used to the observation of the samples after stain it with eosin and hematoxylin stain. The histopathological changes evaluated by using a semi-quantitative scale at several degrees: Severity scores:

1- 0 = Not found.
2- 1+ = Mild.
3- 2+ = Moderate.
4- 3+ = Severe (21).

Statistical analysis

All the data submitted to statistical analysis by using Tukey tests and one-way analysis (ANOVA) at (p< 0.05) wherever by application following formula (mean±standard error) to evaluate the results.

RESULTS

Effect of treatment on kidney function parameters (serum urea, creatinine)

Figure (1) revealed that diclofenac-treated group was showed differences significant at (P < 0.05) increases creatinine and urea in serum compared with –ve control group. Diclofenac plus montelukast treated group associated with significantly ($p < 0.05$) decreased serum urea, and creatinine in comparison with the diclofenac-treated group while vehicle group showed no effect on serum creatinine and urea level.

Figure (2) revealed that the diclofenac-treated group was significantly ($p < 0.05$) decreases serum GSH level when compared with –ve control group. Diclofenac plus montelukast treated group associated with significantly (p *the* < 0.05) increased serum GSH level in comparison with the diclofenac-treated group. Also, the diclofenac-treated group was significantly ($p < 0.05$) increases serum MDA level when compared with –ve control group. Diclofenac plus montelukast treated group was associated with significantly ($p < 0.05$) decreased serum MDA level in comparison with diclofenac. Vehicle group did not affect.

As shown, in table 1 and figure 3, -ve control and vehicle groups presented with normal kidney histopathology figure (3 A and B). Renal tissues of the diclofenac-treated group associated with various degrees of kidney damage (figure 3 C). Montelukast treated group presented with mild Proteinaceous casts accumulation in kidney tubular lumen, mild congestion and no tubular necrosis (figure 3 D)

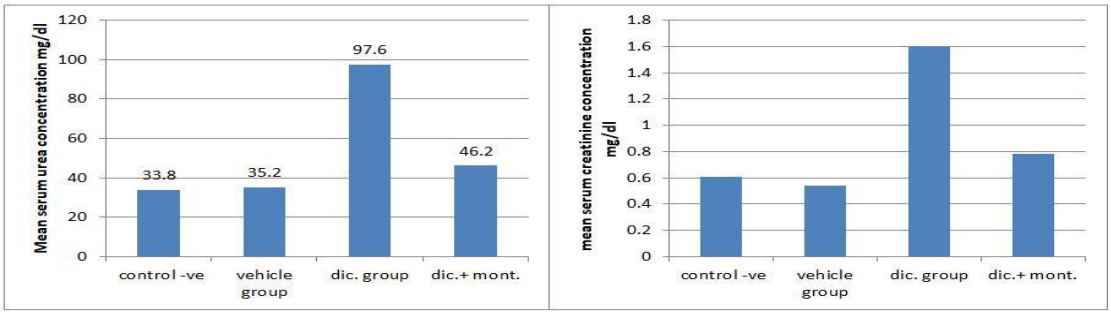

Figure (1): kidney function test A. mean serum urea concentration (mg/dl). B. means serum creatinine concentration (mg/dl).

Effect of treatment on oxidative stress parameters (GSH and MDA)

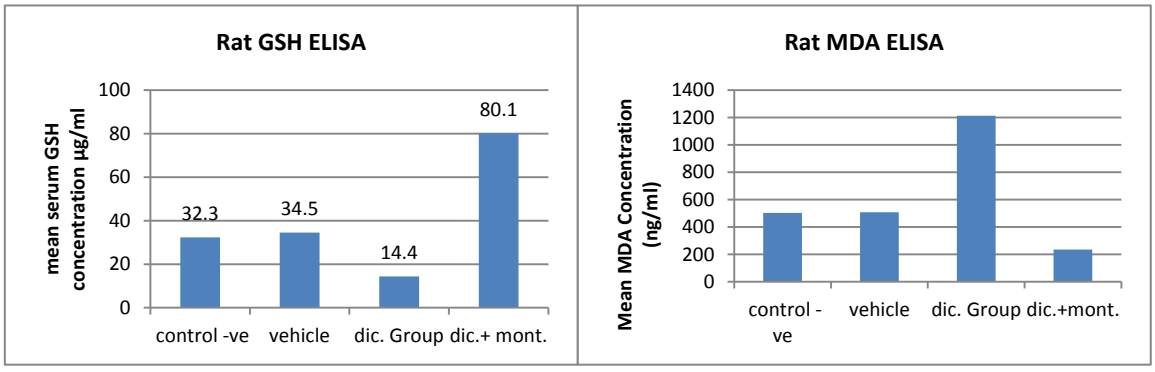

Figure (2): oxidative stress markers A. mean serum GSH concentration (µg/ml). B. mean serum MDA concentration (ng/ml).

Effect of treatment on histopathology examination

Table 1 –ve: control and vehicle groups presented with normal kidney histopathology

Findings	-ve control gr.	Vehicle gr.	Dic. Treated gr.	Dic. Plus Mont. treated gr.
Accumulation of Proteinaceous casts in the tubular lumen	0	0	+2(3/6) +3(3/6)	0(4/6) +1(2/6)
Tubular necrosis	0	0	+1(4/6) +2(2/6)	0(6//6)
Congestion	0	0	+1(2/6) +2(4/6)	0(3/6) +1(2/6)

Rats kidney histology scoring: 0 = Not found; 1+ = Mild; 2+ = Moderate; 3+ = the Severe.

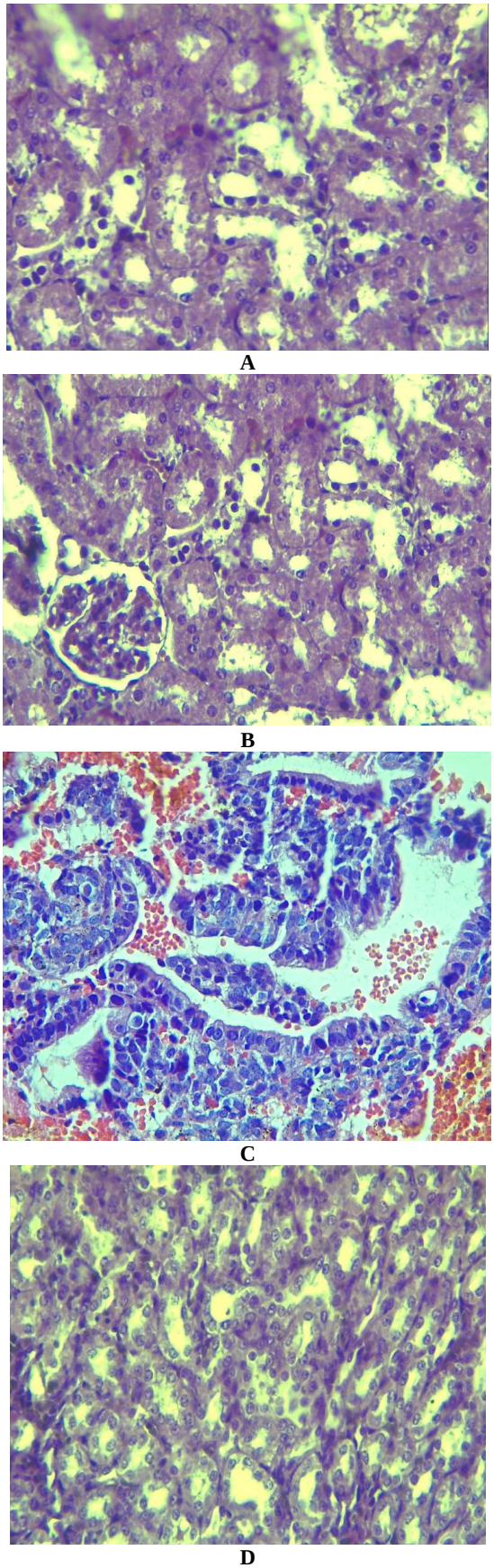

Figure 3: Rat kidney histopathology: A (–ve control), B (vehicle), C (disc. treated gr.), and D (disc. + mont. treated group)

DISCUSSION

The current stud revealed that montelukast treatment associated with significantly decreased serum urea and creatinine in diclofenac-induced acute kidney damage. Otunctemur and presented that there was no difference significantly for urea-creatinine levels [22] while Gad manifested that montelukast treatment returned blood urea nitrogen, as well as serum creatinine that was elevated by cisplatin to a normal level [23]. Additionally, the results revealed that montelukast treated significantly increases serum GSH level and reduced MDA level in the disc. Plus, Mont. Treated group when compared with the disc. Treated one. Suddek concluded that the harmful changes in the kidney tissues and functions that induced by cisplatin administrating and oxidative stress markers were significantly mitigating by montelukast administration [24]. Beytur concluded that Montelukast administration after cisplatin would give positive effects in Cr, BUN and MDA concentration as compared with the control group.

Furthermore, GSH concentration will be decreased due to the treatment of the cisplatin. Montelukast administration elevates GSH levels [25]. Khodir evidenced that montelukast attenuates lipopolysaccharide-induced cardiac injury in rats. By decreasing MDA, and increasing GSH content in heart tissue [26]. Treatment by montelukast will stop the increasing the cytokine formation in kidney injury. The leukotrienes regulate the cytokines and prevent oxidative damage. The cytokines stimuli mastocytes, platelets, macrophages and neutrophils which release large amounts of the toxic free radical or called reactive oxygen substances. These substances caused the cells damage by special mechanisms such as lipid peroxidation and the oxidative of DNA and proteins [27-29]. Also, our data revealed that mont treatment associated with mild histopathological changes when compared with acute kidney damage caused by diclofenac. Kose E concluded that treatment by montelukast after amikacin administration would decrease the nephrotoxic effect on kidney [30]. Sunday also concluded that montelukast had a protective effect against obstructive damage of the kidney (31, 32).

CONCLUSION

The study concluded that montelukast has a protective effect against diclofenac-induced acute kidney damage through its effect on kidney biochemical parameters and oxidative stress markers.

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