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ORIGINAL ARTICLE

The Role of Pentoxifylline in Renal Ischemic Reperfusion Cell Injury and Inflammatory Reaction

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Doustar Yousef, Kazemii Davuod, Nasaghi Habibolah, Zare Hossein, Safarmashaei Saeid: The Role of Pentoxifylline in Renal Ischemic Reperfusion Cell Injury and Inflammatory Reaction

ABSTRACT

Ischemic/reperfusion induced cell death and inflammatory reaction (acute renal failure) is a common clinical problem associated with acute renal failure and renal transplantation. In this study the effects of pentoxifylline on the attenuation of an ischemia-reperfusion injury and inflammatory reaction were examined. Twelve adult mixed breed dogs of both sexes, weighing 10-20 kg, were chosen and then the dogs were assigned randomly into control and treatment groups (n=6).Celiotomy was performed by ventral midline incision. The left kidney was isolated, and then both the renal artery and vein were clamped. After 60 minutes of warm ischemia, the vessels were unclamped and followed by 72 hours of reperfusion, while the right kidney was removed. Blood samples were collected before ischemia and at 24, 48 and 72 hours after ischemia for determination of serum creatinine and BUN level. After 72 hours of ischemia-reperfusion tissue samples from the left kidney were taken for histopathology examination. The treatment group showed lower creatinine, BUN ($P<0.001$ each), cell death ($P<0.05$ each) and of renal inflammatory reactions than did the control group. The result of this study indicates that pentoxifylline alone might play a role in attenuation ischemia-reperfusion cell injury and reduced inflammatory reaction that may contribute to the ischemic renal damage.

Key words: Pentoxifylline, Renal, Ischemic reperfusion, Apoptosis, Necrosis

Introduction

Several studies have examined the role of leukocytes and their surface adhesion molecules and apoptosis in the pathogenesis of post ischemic renal damage. Leukocyte adhesion molecules seem to facilitate polymorphonuclear neutrophils recruitment during reperfusion, being implicated as mediators of renal IRI [5,6]. Renal injury as a result of ischemia reperfusion (I/R) is a major clinical problem and is the most common cause of acute renal failure after renal transplantation, shock, sepsis, and renal artery stenosis. For patients in shock, acute tubular necrosis is associated with a mortality rate of approximately 50%, and little has changed in the past 40 yr [1]. Treatment of I/R injury is still only supportive. Therefore, development of therapeutic interventions to prevent or reduce renal tissue injury after I/R remains the focus of research. Tumor necrosis factor-α (TNF-α) is an important cytokine participating in damage and inflammation in both animal and human renal diseases [2,3]. TNF-α affects differentiation of macrophages into inflammatory cells and primes neutrophils to increase secretary responses and generation of reactive oxygen radicals and NOS. TNF-α also triggers cell death by apoptosis and necrosis. These effects all promote tissue injury in the target organ. Gomez-Chiarri *et al.* [2] have shown that in ADR nephropathy platelet-activating factor (PAF) and TNF-α production precede

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proteinuria. Furthermore, treatment with BN52021 (a PAF antagonist) resulted in both a striking decrease in proteinuria and diminution in glomerular TNF-α and PAF production. Significant correlations between urinary TNF-α levels and both the proteinuria and the clinical activity scores in patients with active renal disease and cellular proliferation have been demonstrated [3]. Pentoxifylline (PTX) is a methylxanthine derivative and phosphodiesterase inhibitor, which inhibits the generation of mRNA for TNF-α in vitro and decreases the in vivo production of TNF-α in humans and in experimental animals [4]. PTX has also been shown to inhibit programmed cell death in short-term cell cultures as well as iNOS enzyme activity in macrophage cell culture [5,6]. Thus, we hypothesized that PTX would be interesting to study in our ADR-induced nephropathy model. We have studied the effects of PTX on TNF-α, proteinuria, and apoptosis in rats with ADR nephropathy Ischemic/reperfusion induced cell death and inflammatory reaction (acute renal failure) is a common clinical problem associated with acute renal failure and renal transplantation. In this study the effects of pentoxifylline on the attenuation of an ischemia-reperfusion injury and inflammatory reaction were examined.

Statically Analysis:

Material and methods

Twelve adult mixed breed dogs of both sexes, weighing 10-20 kg, were chosen and then the dogs were assigned randomly into control and treatment groups (n=6). Celiotomy was performed by ventral midline incision. The left kidney was isolated, and then both the renal artery and vein were clamped. After 60 minutes of warm ischemia, the vessels were unclamped and followed by 72 hours of reperfusion, while the right kidney was removed. Blood samples were collected before ischemia and at 24, 48 and 72 hours after ischemia for determination of serum creatinine and BUN level. After 72 hours of ischemia-reperfusion tissue samples from the left kidney were taken for histopathology examination.

Results and discussion

Ischemia/reperfusion injury (IRI) is an important cause of acute renal failure in native kidneys and allograft [1]. Cellular and molecular responses of the kidney to acute ischemic injury are complex and not fully understood [2–4]. The treatment group showed lower creatinine, BUN ($P<0.001$ each), cell death ($P<0.05$ each) and of renal inflammatory reactions than did the control group. All results of present study by following figures has been shown.

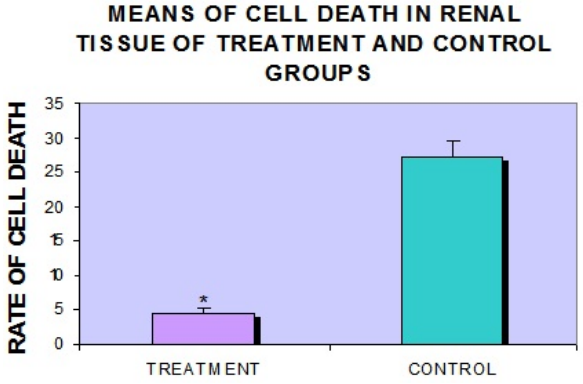

Fig. 1: Ordinary means of cell death in renal tissue of treatment and control groups. Data present with form of Mean±SEM and*P<0.005 compression between groups.

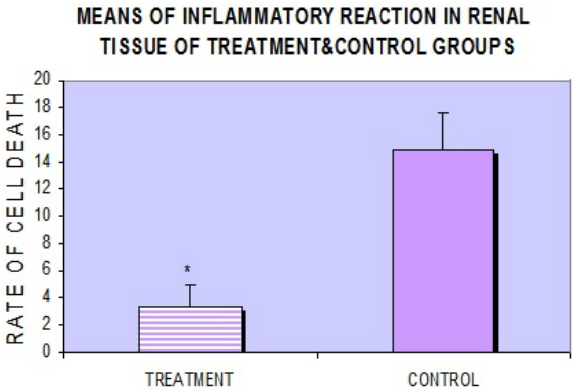

Fig. 2: Ordinary means of inflammatory reaction in renal tissue of treatment and control groups. Data present with form of Mean±SEM and*P<0.005 compression between groups.

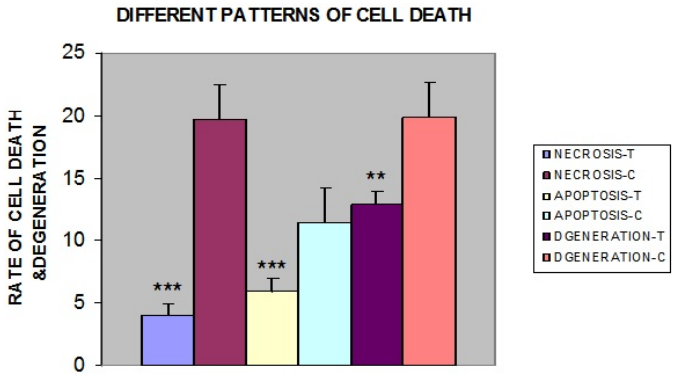

Fig. 3: Compression of necrosis and apoptosis changes in treatment and control groups (n=6). Data present with form of Mean±SEM. ***P<0.005 and **P<0.01 on compression between groups.

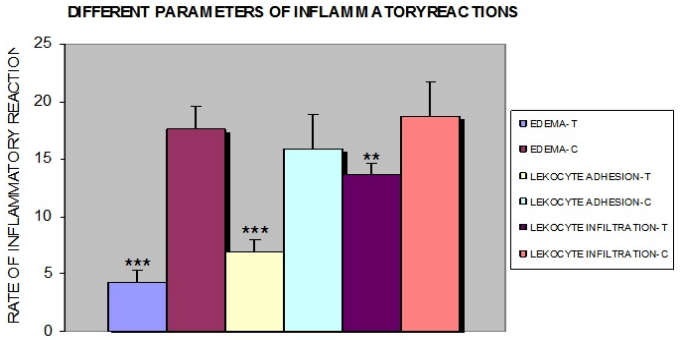

Fig. 4: Compression inflammatory reactions in treatment and control groups (n=6). Data present with form of Mean±SEM. ***P<0.005 and **P<0.01 on compression between groups.

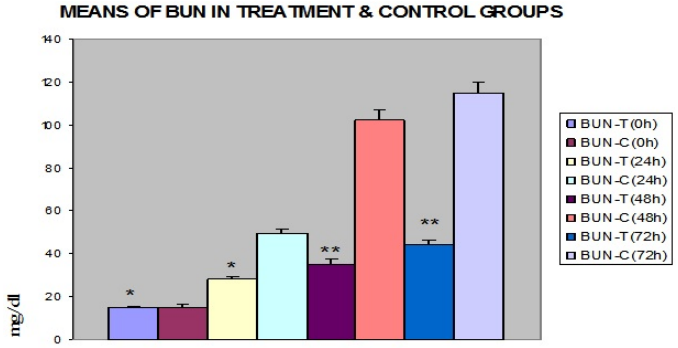

Fig. 5: Compression of BUN changes in treatment and control groups (n=6). Data present with form of Mean±SEM. ***P<0.005, **P<0.01 and *P>0.05 in compression between groups.

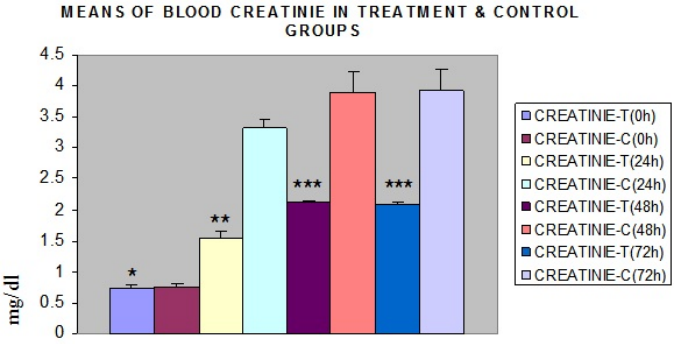

Fig. 6: Compression of creatinine changes in treatment and control groups (n=6). Data present with form of Mean±SEM. ***P<0.005, **P<0.01 and *P>0.05 in compression between groups.

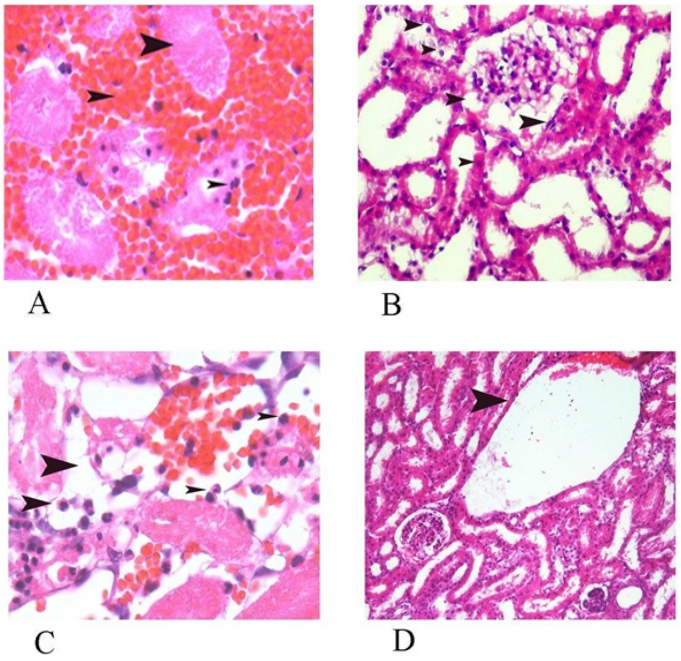

Fig. 7: A. Photomierograph of renal tubular neerosis, heamorrhage and leukocyte infiltration in conttrol group H&E(×100). B. Photomicrograph of renal tubular in treatment group with a few degeneration. H&E(×40). C. Photomicrograph of renal tubular in control group with leu-kocyte infiltration and tubular cells necrosis H&E(×100). D. Photomicrograph of renal tubular in treatment group without leukocyte infiltration and tubular cells necrosis H&E(×40)

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