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SCIENTIFIC ARTICLE

Comparison of the effects of dexmedetomidine administered at two different times on renal ischemia/reperfusion injury in rats

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Abstract
Background and objectives: We investigated the effect of dexmedetomidine on ischemic renal failure in rats.
Methods: In the present study, 26 male adult Wistar albino rats weighting 230–300 g were randomly separated into four groups: sham-operated ($n = 5$), ischemia reperfusion (IR) (IR group, $n = 7$), IR/reperfusion treatment with dexmedetomidine (Dex. R group, $n = 7$) and IR/pre-ischemic treatment with dexmedetomidine (Dex. I group, $n = 7$). In the first group, sham operation was achieved and renal clamps were not applied. For the IR group, renal ischemia was induced by occlusion of the bilateral renal arteries and veins for 60 min followed by reperfusion for 24 h. For the Dex. R and Dex. I groups, the same surgical procedure as in the IR group was performed, and dexmedetomidine (100 mcg/kg intraperitoneal) was administrated at the 5th min after reperfusion and before ischemia. At the end of reperfusion, blood samples were drawn, the rats were sacrificed, and the left kidney was processed for histopathology.
Results: The blood urea nitrogen (BUN) levels in groups Dex. R and Dex. I were significantly lower than in the IR group ($p = 0.015$, $p = 0.043$), although urine flow was significantly higher in group Dex. R ($p = 0.003$). The renal histopathological score in the IR group was significantly higher than in the other groups. There was no significant difference between the Dex. R and Dex. I groups.

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Conclusions: The results were shown that administration of dexmedetomidine reduced the renal IR injury histomorphologically. Administration of dexmedetomidine in the reperfusion period was considered as more effective due to increase in urinary output and decrease in BUN levels.

Introduction

Acut renal failure is an acute ischemic response of the kidneys occurring due to hypoperfusion secondary to hypotension, hypovolemia and dehydration as well as ischemia/reperfusion (IR) injury presenting with high mortality and morbidity in clinical practice.[1–3]

Increased microvascular permeability, interstitial edema, impaired vasoregulation, inflammatory cell infiltration, parenchymal cell dysfunction, and acute tubular necrosis (ATN) have been shown in the histopathological studies related to renal IR injury.[4–6] These changes peaked at the 24th hours after reperfusion and they correlated with increased levels of blood urea nitrogen (BUN) and serum creatinine (Cr) which they are used as an indicator for renal function in clinical settings.[7,8]

Dexmedetomidine is an active dextro-stereoisomer of medetomidine and selective α_2-adrenoceptor agonist.[9] Dexmedetomidine reduces the plasma levels of catecholamines,[10,11] provides hemodynamic stability during surgery[12,13] and increases the urinary flow rate.[14] Villela et al.[15], and Frumento et al.[16] showed that dexmedetomidine caused aqueous diuresis by reducing central vasopressin secretion and significantly improved renal functions postoperatively in their both clinical and experimental studies. Kocoglu et al.[17] have been studied the effects of dexmedetomidine on renal IR injury. They found improved histological scores at the end of the 45 min of reperfusion following 1 h of complete renal ischemia.

The aim of this study was to examine the histopathologic and biochemical effects of dexmedetomidine administrated two different times (before ischemia and at the beginning of reperfusion) on renal IR injury at 24th hour of reperfusion.

Materials and methods

Twenty-six adult Wistar albino rats weighing 230–300 g were used in this study. The animals were housed in a light controlled room with a 12-h light/dark cycle and allowed access to food and water. Experimental protocols and animal care methods in the experiment were approved by the Experimental Animal Research Committee of our institution.

Rats were divided into four groups: sham operated group ($n = 5$), IR/untreated group (IR group, $n = 7$), reperfusion treatment with dexmedetomidine (100 μg/kg at 5 min after the reperfusion, ip) (Dex. R group, $n = 7$), preischemic treatment with dexmedetomidine (100 μg/kg at 5 min before the ischemia, ip) (Dex. I group, $n = 7$). The rats were anesthetized with ketamine (50 mg/kg ip) and xylazine hydrochloride (10 mg/kg ip) and bilateral renal pedicles were exposed after laparotomy. After anesthesia, the rats were heated with a heating lamp to maintain a rectal body temperature of 37 °C. Isotonic saline solution accounted of 25% of rat body weight was given intraperitoneally before closure of abdomen. For ischemia and reperfusion injury induced, bilateral renal pedicle occlusion was performed with hemostasis clip for 60 min. At the end ischemic period, the clips were removed for blood reperfusion. In sham operated group, bilateral renal pedicles were exposed without any intervention after laparotomy. The animals exposed to 60 min ischemia were housed in metabolic cages 24 h after reperfusion; 24 h urine samples were collected. At the beginning of study, 1 ml of blood sample was drawn from the lateral tail vein for the measurement of basal renal function parameters before abdominal incision. At the end of reperfusion, the animals were anesthetized, the blood samples were drawn from the right atrium for the measurement of renal function parameters and left kidneys were excised. The kidneys were fixed in 10% buffered formalin and embedded in paraffin wax, cut at 4–5 μm and stained with hematoxylin and eosin for histological studies using light microscope.

Histopathologic changes were analyzed for mononuclear cell infiltration, erythrocyte extravasation, capillary dilatation, renal corpuscle morphology, vacuolization of proximal tubules, apoptosis, loss of tubular brush border, tubular dilatation and cast formation. Tubulointersititial injury was scored as follows: 0 = none, 1 = 0–10%, 2 = 11–25%, 3 = 26–45%, 4 = 46–75%, and 5 = 76–100%.[18] The scoring of the histological data was performed by blind investigator.

Blood urea nitrogen and plasma Cr levels were measured. Fractional sodium excretion (FA_{Na}) and Cr clearance (CCr) were calculated from the following formula: $FA_{Na} = UNaV/(PNa \times \text{creatinine clearance}) \times 100$ (UNaV: urinary sodium, PNa: plasma sodium);[19] CCr = (Urine Cr × urine volume)/(Plasma Cr × time).[20]

For statistical analysis, SPSS 15.0 (Statistical Package for the Social Sciences ver. 15,Chicago, IL, USA) was used. All data were expressed as mean ± standard deviation (mean ± SD). Univariate analysis was conducted via Mann–Whitney *U* test to compare two independent groups. The level of statistical significance was accepted as $p < 0.05$.

Results

A total of 26 rats were included in the study. One rat in the IR group died during the ischemia period and was excluded from the study; thus, 25 subjects completed the study. The histopathological scores of the rats in all groups are presented in Table 1.

The histomorphologic injury scores of the sham operated group were statistically significant lower than IR, Dex. I and