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Original Research

Effects of dexmedetomidine pretreatment on rats with sepsis-induced acute kidney injury and miR-146a expression

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Abstract: The current research aimed to study the effects of dexmedetomidine (DEX) pretreatment on rats with sepsis-induced acute kidney injury (SAKI) and miR-146a expression. The model of SAKI was established through the tail vein injection of lipopolysaccharide (LSP). We used an automatic biochemical analyzer to detect serum urea nitrogen (BUN) and creatinine (Cre) levels. The expression levels of urine KIM-1 and NGAL and serum IL-1β and IL-6 were analyzed by enzyme-linked immunosorbent assay (ELISA). The content and activity of superoxide dismutase (SOD) were detected by the xanthine oxidase method. The content of malondialdehyde (MDA) was determined by the thiobarbituric acid (TBA) method. Reactive oxygen species (ROS) was detected by fluorescent probe DCFH-DA. Catalase (CAT) was detected by potassium permanganate titration. The expression level of miR-146a in the renal tissue and serum was detected by RT-PCR. The expression levels of Nrf2 and HO-1 proteins were detected by Western blot. Compared with those in the model group, rats in the DEX group had significantly lower expression levels of serum BUN, Cre, IL-1β, and IL-6, and oxidant markers MDA and ROS, but significantly higher expression levels of miR-146a and antioxidant markers SOD and CAT. DEX pretreatment could improve the kidney morphology, injury severity, and Nrf2 and HO-1 proteins of rats with SAKI. In conclusion, DEX can improve oxidative stress and inflammatory responses in rats with SAKI, reduce the severity of the renal injury, and up-regulate the expression level of miR-146a.

Key words: Dexmedetomidine; Rats with SAKI; miR-146a expression.

Introduction

Sepsis, which is an uncontrolled inflammatory response caused by infection or very serious trauma, has a high incidence and extremely high mortality (1). The disease may affect myocardial contractility and then inhibit the oxygen inhalation of organs, further leading to septic shock and multiple organ dysfunction syndrome (MODS), which are the most important causes of death in the intensive care unit (ICU) patients (2, 3). A previous study has shown that kidney is one of the organs most prone to infection and injury in septic patients, and about 50% of the patients experience sepsis-induced acute kidney injury (SAKI), which poses a serious threat to their lives and health (4). Currently, acute kidney injury (AKI) can be regulated by antibiotics or immunotherapy, both of which, however, cannot reduce the mortality of the disease (5). In addition, the mortality of patients with SAKI has been shown to be 70% (6). Therefore, it is urgent to effectively prevent and intervene in SAKI.

miRNA is a factor widely presented in eukaryotic cells and a serum marker significant for the diagnosis of many diseases (7). As a nuclear factor-κB (NF-κB)-dependent gene, miR-146a inhibits the development of inflammatory responses by regulating tumor necrosis factor receptor-associated factor 6 (TRAF-6) and interleukin-1 receptor-associated kinase 1 (IRAK-1) (8). Its expression up-regulates in the serum of septic patients (9). Dexmedetomidine (DEX) is a selective α2-adrenergic receptor agonist mainly used for sedation and analgesia (10). It inhibits the release of neutrophils or other inflammatory cytokines, which avoids lipid peroxidation and then protects multiple organs such as the heart, lung, and kidney (11-20).

Therefore, the effects of DEX on rats with SAKI and on miR-146a expression level were observed in this study, to explore the effects on SAKI and the relationship with miR-146a expression level, so as to provide a new research direction for the treatment of sepsis.

Materials and Methods

Experimental animals and materials

Sixty clean Sprague Dawley (SD) rats (purchased from the Experimental Animal Center of Zhongshan University), who had a body mass of 195-240 g, were enrolled and fed in an environment with a temperature of 20-25 ℃ and the relative humidity of 40-70%. They were free to food and water, with normal circadian rhythms. DEX (specification: 200μg/mL, Batch No.: 15092932) was purchased from Jiangsu Hengrui Medi-

cine Co., Ltd. Lipopolysaccharide (LSP) (Batch No.: 037M4015V) was purchased from Sigma, Germany. Chloral hydrate (SFDA Approval Number: H37022673) was purchased from Qingdao Yulong Seaweed Co., Ltd. Creatinine (Cre) (Batch No.: EY-(Ela)-0467) was purchased from Shanghai Yiyan Biological Technology Co., Ltd. Blood urea nitrogen (BUN) (Batch No.: JL20491) enzyme-linked immunosorbent assay (ELISA) kit was purchased from Shanghai Jianglai Biotechnology Co. Ltd. Nrf2, HO-1, and β-actin (primary antibodies) were purchased from Abcam, USA. Horseradish peroxidase (HRP)-labeled goat anti-rabbit IgG (secondary antibody) was purchased from Wuhan Boster Biological Technology Co., Ltd. IL-1β (ml001814) and IL-6 (ml002293) ELISA kits were purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd. SYBR Green MasterMix (Batch No.: A8605) was purchased from ABI, USA.

Grouping and modeling

Rats were randomized into a control group, a model group, and a DEX group (n=20 each). LPS induction was used to establish the model of rats with SAKI. All rats were intraperitoneally injected with chloral hydrate (0.3mL/100 g) with a concentration of 10%. After that, rats in the model and DEX groups were given the tail vein injection of LSP (5mg/kg), while those in the control group were injected with the same dose of normal saline. Rats in the DEX group were intraperitoneally injected with DEX (100 μg/kg) 30min before LSP injection, while those in the control and model groups were intraperitoneally injected with the same dose of normal saline 30min before modeling. After the modeling, the rats in the three groups continued to be conventionally fed for 24 h, and then subsequent experiments were carried out.

Specimen collection

After modeling for 24 h, the rats' blood was extracted through the abdominal aorta and centrifuged at 2000 r/min for 10min to separate the serum, which was then collected for the detection of serum indices. After that, the rats were killed by cervical dislocation and their two kidneys were taken out. The left one was fixed with 10% formalin, embedded with paraffin, and then sliced and stained. Finally, it was used for histopathological analysis. The right renal tissue was used for the subsequent detection of indices.

Detection of indices

Detection of indices of renal injury and oxidative stress responses

Serum Cre and BUN are important indices for evaluating renal injury. Kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) has been also known as biomarkers for renal injury (Shlipak&Day, 2013). By an automatic biochemical analyzer, the expression levels of serum BUN and Cre were detected. The expression levels of urine KIM-1 and NGAL were analyzed by ELISA. The content and activity of superoxide dismutase (SOD) were detected by the xanthine oxidase method. The content of malondialdehyde (MDA) was determined by the thiobarbituric acid (TBA) method. Reactive oxygen species (ROS) was detected by fluorescent probe DCFH-DA. Catalase (CAT) was detected by potassium permanganate titration. All the steps were carried out in accordance with the instructions of the kits. The expression levels of inflammatory markers IL-1β and IL-6 were analyzed by ELISA according to the instructions of the kits.

Western blot detection of Nrf2 and HO-1 proteins

Part of the right renal tissue of each rat was ground to extract total protein using the RIPA lysis method. BCA was used for quantitative protein detection, after which the protein concentration was adjusted to 5μg/μL. Then, the protein separation was occurred with electrophoresis with 12% SDS-PAGE, then the protein transferred to PVDF membrane, and sealed with 5% skimmed milk powder at room temperature for 2h. Next, rat monoclonal antibodies [Nrf2 (1: 1000), HO-1 (1: 1000), and β-actin (1:1000)] were respectively added and sealed overnight at 4 ℃. After that, HRP-labeled goat anti-rabbit IgG (secondary antibody) (1: 2000) was added and incubated at 37 ℃ for 1h. Finally, the protein was luminesced with ECL and developed. The experiment was repeated 3 times.

RT-PCR detection of miR-146a expression level

The frozen renal tissue of each rat was ground to extract total RNA from the serum and renal tissue using Trizol reagents. The ultraviolet spectrophotometer was used to detect its purity and concentration. SYBR-Green Realtime PCR Master Mix was used to reversely transcribe the total RNA of miR-146a, with steps carried out in strict accordance with the manufacturers' kits. Then, PCR amplification was conducted. The system was as follows: 1μL of cDNA, each 0.4 μL of upstream and downstream primers, 10μL of 2×SYBR-Green Realtime PCR Master mix, 0.4 μL of Passive Reference Dye (50X), and ddH_2O finally added to make up to 20μL. The conditions were as follows: pre-denaturation at 95 ℃ for the 30s, then cycling (at 94 ℃ for 45s and 55 ℃ for 40s) for 40 times, and a final extension at 70℃ for 30s. U6 was used as an internal reference. The sequences of miR-146a were F: 5'-CAGTGCGTGTCGTGGAGT-3' and R: 5'-GGGTGAGAACTGAATTCC-3'. The sequences of U6 were F: 5'-GCTTCGGCAGCACATATACTAAAAT-3' and R: 5'-CGCTTCACGAATTTGCGTGTCAT-3'. The experiment was repeated 3 times.

Statistical methods

In this study, in order to statistical analysis, we used the SPSS 20.0. For plotting of figures, the GraphPad Prism 6 was used. Measurement data were expressed by mean ± standard deviation (SD±meas) and analyzed by the t-test. The comparison of means was accomplished using an independent t-test, the comparison between several groups was performed using one-way analysis of variance, and the LSD test performed to pairwise comparison.

Pearson was used for correlation analysis. When $P< 0.05$, the difference was statistically significant.

Results

Kidney morphological changes

After modeling for 24h, rats in the control group had clear and complete renal tissue structure, without renal tissue edema and inflammatory cell infiltration. Rats in the model group had significantly declined clarity of the renal tissue structure, and significant renal tissue edema and inflammatory cell infiltration. Additionally, in the model group rats, the glomerular number reduced, glomerular volume increased, and even some glomeruli experienced hyaline degeneration. Scattered bleeding points and inflammatory cell infiltration could be seen in renal interstitium. Luminal stenosis, the swelling and exfoliation of epithelial cells, and the brush border disappearance of proximal convoluted tubules occurred in renal tubules. Compared with those in the model group, rats in the DEX group had significantly fewer lesions in glomeruli, renal interstitium, and renal tubules, and inflammatory cells in the renal tissue.

Improvement of renal injury by DEX

The expression levels of serum Cre and BUN and urine KIM-1 and NGAL in the model group were significantly higher than the control and DEX groups (P<0.05). The levels in the DEX group were significantly higher than the control group (P< 0.05) (Figures 1A-1D).

Improvement of oxidative stress responses by DEX

The activity of oxidant markers MDA and ROS in the model group were significantly higher than the control and DEX groups, while the activity of antioxidant markers SOD and CAT were significantly lower than the control and DEX groups (P< 0.05). The activity of MDA and ROS in the DEX group was significantly higher than the control group, while the activity of SOD and CAT was significantly lower than the control group (P< 0.05) (Figures 2 A-D).

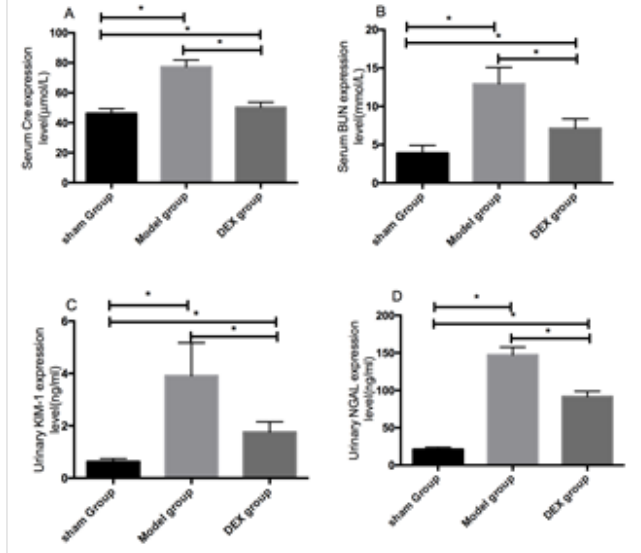

Figure 1. All comparisons were statistically significant. **(A)** The expression level of serum Cre in the model group was higher than the control and DEX groups, and the level in the DEX group was higher than the control group. **(B)** The expression level of serum BUN in the model group was higher than the control and DEX groups, and the level in the DEX group was higher than the control group. **(C)** The expression level of urine KIM-1 in the model group was higher than the control and DEX groups, and the level in the DEX group was higher than the control group. **(D)** The expression level of urine NGAL in the model group was higher than the control and DEX groups, and the level in the DEX group was higher than the control group.

Improvement of inflammatory responses by DEX

The expression levels of serum inflammatory markers IL-1β and IL-6 in the model group were significantly higher than the control and DEX groups (P< 0.05). The levels in the DEX group were significantly higher than the control group (P< 0.05) (See Figures 3).

Expression levels of Nrf2 and HO-1 proteins in renal tissue

The expression levels of Nrf2 and HO-1 proteins in

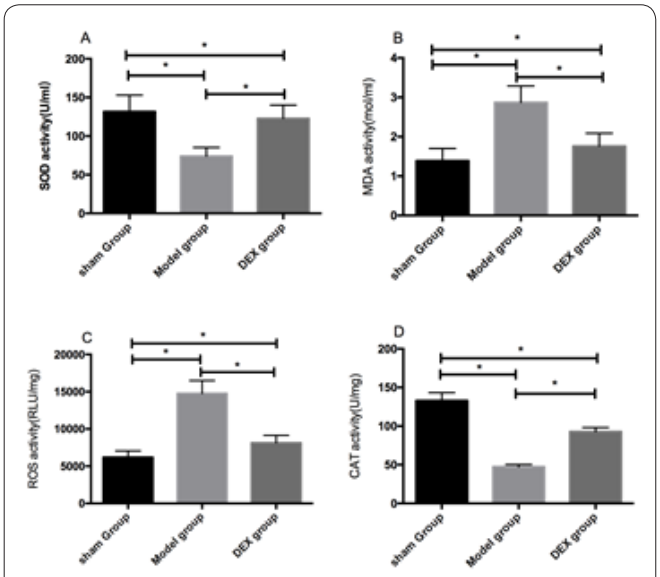

Figure 2. All comparisons were statistically significant. **(A)** The activity of SOD in the model group was lower than the control and DEX groups, and the activity in the DEX group was lower than the control group. **(B)** The activity of MDA in the model group was higher in the control and DEX groups, and the activity in the DEX group was higher than the control group. **(C)** The activity of ROS in the model group was higher than the control and DEX groups, and the activity in the DEX group was higher than the control group. **(D)** The activity of CAT in the model group was lower than the control and DEX groups, and the activity in the DEX group was lower than that in the control group. * indicates P< 0.05.

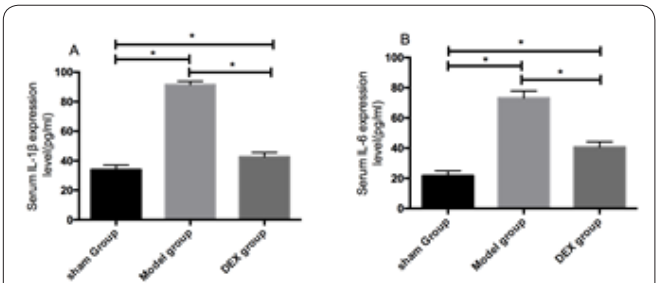

Figure 3. All comparisons were statistically significant. **(A)** The expression level of IL-1β in the model group was higher than the control and DEX groups, and the level in the DEX group was higher than the control group. **(B)** The expression level of IL-6 in the model group was higher than the control and DEX groups, and the level in the DEX group was higher than the control group. * indicates P<0.05.

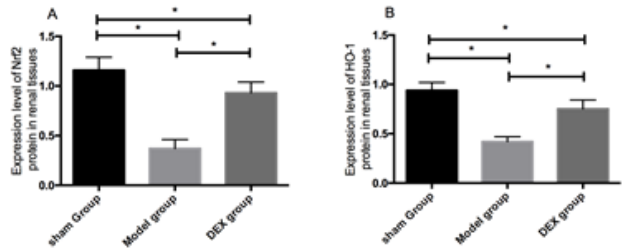

Figure 4. All comparisons were statistically significant. **(A)** The expression level of Nrf2 protein in the renal tissue in the model group was lower than the control and DEX groups, and the level in the DEX group was lower than the control group. **(B)** The expression level of HO-1 protein in the renal tissue in the model group was lower than the control and DEX groups, and the level in the DEX group was lower than the control group. * indicates P <0.05.

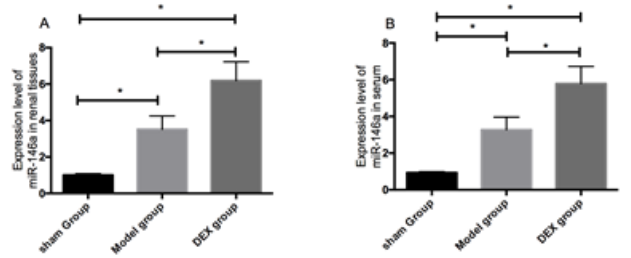

Figure 5. All comparisons were statistically significant. **(A)** The expression level of miR-146a in the renal tissue in the model group was higher than the control group, and the level in the DEX group was higher than the model group. **(B)** The expression level of miR-146a in the serum in the model group was higher than the control group, and the level in the DEX group was higher than the model group.

the renal tissue in the model group were significantly lower than the control and DEX groups (P< 0.05). The levels in the DEX group were significantly lower than the control group (P< 0.05). See Figures 4A-B.

The expression level of miR-146a in renal tissue and serum

The expression level of miR-146a in the renal tissue and serum in the model group was significantly higher than the control group (P< 0.05). The level in the DEX group was significantly higher than the model group (P< 0.05). See Figures 5A-5B.

Correlation of serum miR-146a expression level with IL-1β and IL-6 expression levels in DEX group

The expression level of serum miR-146a was negatively correlated with the expression levels of IL-1β and IL-6 in the DEX group (P< 0.05). See Figures 6A-6B.

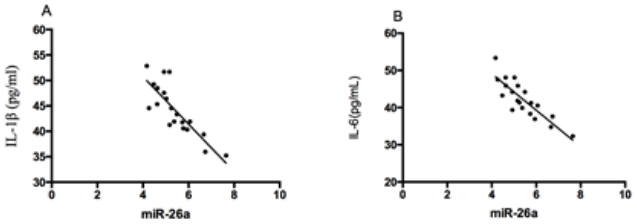

Figure 6. (A) The expression level of serum miR-146a was negatively correlated with the expression level of IL-1β (r=-0.831, P< 0.05). **(B)** The expression level of serum miR-146a was negatively correlated with the expression level of IL-6 (r=-0.856, P< 0.05).

Discussion

As a clinically common and serious infectious disease, sepsis is one of the key causes of patient deaths, especially for ICU patients (21). One of its common complications is AKI which has extremely complex pathophysiology (22). A study has shown that AKI is closely related to oxidative stress and inflammatory responses, but the mechanism of SAKI remains unclear (23).

In this experiment, the rat model of SAKI established through the tail vein injection of LSP, and the protective effect of DEX on AKI was discussed. The renal lesion and injury severity in the DEX group were significantly lighter than the model group; the expression levels of serum Cre and BUN and urine KIM-1 and NGAL in the DEX group were significantly better than the model group. This suggests that DEX can relieve and treat rats with SAKI to some extent. According to a study, DEX protects multiple organs by inhibiting oxidative stress and inflammatory responses (24). Therefore, the oxidant and antioxidant markers and inflammatory cytokines were detected. Compared with those in the model group, rats in the DEX group had significantly lower activity of MDA and ROS, but the significantly higher activity of SOD and CAT. IL-1β and IL-6 are highly representative inflammatory cytokines (25), and their expression levels in the DEX group were significantly improved compared with those in the model group. These findings indicate that DEX can inhibit oxidative stress and inflammatory responses in rats with SAKI, thereby improving their renal injury. We also speculated that DEX may protect the kidney by regulating the balance between pro-oxidant and antioxidant responses. According to studies, DEX significantly improves anti-oxidative stress and anti-inflammatory responses in septic patients (25). It inhibits the apoptosis of renal cells through activating α2AR, which is also the main mechanism of its protective effect on the kidney (26). However, we did not discuss this in detail, which will be further explored in the following studies. Nrf2, whose activation has been clearly shown to inhibit the development and progression of SAKI (27), is an important coordination factor in anti-oxidative and anti-inflammatory damage in cell protection (28). HO-1 is one of the major antioxidant genes regulated by Nrf2. In this study, the expression levels of Nrf2 and HO-1 proteins in the DEX group were significantly higher in the model group. This demonstrates that DEX may inhibit the oxidative stress responses of rats with SAKI by stimulating the Nrf2/HO-1 pathway, thus improving their renal injury, which was consistent with the findings of Song and others (29).

The role of miRNA in various diseases, especially in malignant tumors, has been valued (30, 31). NF-kB-dependent miR-146a is a popular miRNA for regulating inflammatory responses, and its expression is up-regulated by the stimulation of human monocytic leukemia through LSP or IL-1β (32). In this study, the expression level of miR-146a in the renal tissue and serum in the model group was significantly higher than that in the control group, the reason may be that the development

of LSP-induced inflammatory responses stimulates the expression. The expression level of miR-146a in the DEX group was significantly higher than the model group, which indicates that the reduction of renal injury in rats with SAKI may be related to the further up-regulation of miR-146a expression level. According to the correlation analysis, the expression level of serum miR-146a was negatively correlated with the expression levels of inflammatory cytokines. According to previous studies, the up-regulation of miR-146a expression level can inhibit the inflammatory responses of LSP-induced acute lung injury (33). miR-146a is an NF-κB-dependent factor. NF-κB stimulates the production of a large number of inflammatory cytokines and induces the up-regulation of miR-146a expression level, which negatively regulates the TLRs/NF-kB pathway, thus inhibiting inflammatory responses (34, 35). This is also the reason why the expression level of miR-146a in the renal tissue and serum in the DEX group was significantly higher than the model group (34-37).

In summary, DEX can improve oxidative stress and inflammatory responses in rats with SAKI, and reduce their renal injury. Its inhibition of inflammatory responses may be realized by up-regulating the expression level of miR-146a. However, there are still limitations to this study. For example, the mechanism of miR-146a inhibiting inflammatory responses in rats with SAKI was not fully explored, which will be investigated in future studies.

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Availability of data and materials
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions
JN, JH, LK and SY led the conception and design of this study. JN, JH, ZZ and LW were responsible for the data collection and analysis. JH and LK were in charge of interpreting the data and drafting the manuscript. JN and SY made revision from a critical perspective for important intellectual content. The final version was read and adopted by all the authors.

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Suzhou Kowloon Hospital, China.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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