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Effects of Dexmedetomidine on Hepatic Ischemia Reperfusion Injury in Rats with Cholestasis and Liver Fibrosis

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Abstract: Back ground: Liver complicated with cholestasis and fibrosis is vulnerable to ischemia reperfusion injury (IRI). Objectives: To investigate the effects of dexmedetomidine on hepatic ischemia reperfusion injury in rats with cholestasis and liver fibrosis. Material and Methods: Model of rats with cholestasis and liver fibrosis is established by bile duct ligation (BDL) for 18 days. Thirty-two male modeled SD rats were randomized into four groups (n=8): Group S: rats underwent laparotomy but the hepatic pedicle was not occluded. Group IRI: the hepatic pedicle was occluded for 30min. Group D10: dexmedetomidine 10μg/kg was injected intraperitoneally before hepatic ischemia. Group D100: dexmedetomidine 100μg/kg was injected intraperitoneally before hepatic ischemia. Blood samples were obtained for analysis of total billirubin (TBIL), direct billirubin (DBIL), aspertate transaminase (AST), alanine transaminase (ALT), and tumor necrosis factor-α (TNF-α). Liver tissues were obtained for analysis of superoxide dismutase (SOD) and malondialdehyde (MDA), and were observed after hemotoxylin-eosin (HE) or Masson staining for histopathological assessment. Results: TBIL and DBIL values were not significantly different between four groups ($P > 0.05$). AST, MDA and TNF-α values in group IRI, D10 and D100 were significantly higher than in group S, while SOD value were lower ($P < 0.05$), AST, MDA and TNF-α values in group D10 and D100 were significantly lower than in group IRI, while SOD values were higher ($P < 0.05$). The degrees of bile duct proliferation and fibrosis in liver tissues in four groups were similar. In group IRI, there were severe inflammatory cells infiltration, hepatocellular swelling and even local necrosis in liver tissue, but injuries in group D10 and D100 was moderate. Conclusions: Dexmedetomidine may attenuate hepatic IRI in rats with cholestasis and liver fibrosis, possibly by up-regulation of SOD activity and down-regulation of TNF-α expression.

Keywords: Dexmedetomidine, Liver, Ischemia Reperfusion Injury, Cholestasis, Fibrosis

1. Introduction

Liver resection is widely used to treat with some kinds of liver diseases such as hepatocellular carcinoma, hilar cholangiocarcinoma and hepatolithiasis [1-3]. To reduce blood loss and transfusion in liver resection, surgeons always perform Pringle maneuver to occlude the liver's vascular support, however, this procedure may cause hepatic ischemia reperfusion injury (IRI) [4-5]. Moreover, patients with hilar cholangiocarcinoma or hepatolithiasis may have severe obstructive jaundice, biliary tract infection, and cholestatic liver cirrhosis, thus also triggers inflammatory response and induces ductular proliferation and liver fibrosis, these put the liver more sensitive to IRI [2, 6].

Studies showed that oxidative stress and inflammatory response play a major role in hepatic IRI. The early phase of liver injury after reperfusion is characterized by the activation of Kupffer cells (KC). Activated KCs produce reactive oxygen species (ROS) and numerous inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin 1 (IL-1). ROS results in a rapid depletion of superoxide dismutase (SOD) and subsequent tissue injury, it also attack a variety of cellular components, including DNA, proteins and membrane lipids, lipid peroxidation by ROS results in accumulation of malondialdehyde (MDA) [7]. TNF-α is a cytokine involved in inflammation, it leads to a cascade of processes which stimulates neutrophil adhesion to hepatic sinusoidal cells and damages both hepatocytes and endothelial cells [8]. Moreover, patients with obstructive jaundice or cirrhosis frequently suffer from postoperative complications such as liver dysfunction or liver failure, evidences showed that cholestasis and consequent liver fibrosis has been associated with an augmented generation of ROS and peroxidation products, a reduced anti-oxidative capacity, increased mitochondrial dysfunction, accumulation of neutrophils, and activation of KCs, these defects exacerbate liver damage during IRI [9-10]. Therefore, it is extremely important to protect this marginal liver from IRI.

Dexmedetomidine is a highly selective α_2-adrenergic recepter (α_2-AR) agonist, it is widely used as an adjunct to anesthesia [11]. Previous studies demonstrated that dexmedetomidine is also a promising drug to protect organs from IRI, the anti-oxidative and anti-inflammatory property of the drug played an important role in attenuating hepatic IRI both in experimental and clinical trials [12-14]. However, cholestasis and liver fibrosis are frequently associated with pre-existing oxidative stress, inflammatory response and hepatocytes damage, thus put the liver more vulnerable to IRI, to the best of our knowledge, the effects of dexmedetomidine on IRI in the marginal liver is still remain unclear. The present study was to investigate the effects of dexmedetomidine on hepatic IRI in rats with cholestasis and liver fibrosis.

2. Materials and Methods

2.1. Animals

This study protocol was approved by the Ethics Committee of Experimental Animals of Hunan Provincial People's Hospital. Male Sprague-Dawley rats (Hunan SJA Laboratory Animal Co, Ltd., China) weighing 150 to 180g were housed in a controlled environment with 12 h light and dark cycles, and automatically adjusted temperature (22±2°C). All rats were fed on a standard diet with water and food.

2.2. Rat Model of Cholestasis and Liver Fibrosis

Rats with cholestasis and liver fibrosis were established by bile duct ligation (BDL) as Karavias et al [15]. previously described. After rats were anesthetized by 3% Pentobarbital Sodium (50mg/kg intraperitoneally, Sigma-Aldrich Co.), the abdomens were opened, the common bile duct of each one was ligated with two 5-0 silk sutures and transected between the ligatures. After the abdomens were closed, the rats were taken to the animal house again and kept for 18 days, until cholestasis and liver fibrosis occurred.

2.3. Hepatic Ischemia Reperfusion Injury

On day 18, the modeled rats were laparotomized again under anesthesia with Pentobarbital Sodium administration as before. A midline incision (3cm in length) was done in the upper abdomen, portal vein and hepatic artery was occluded by an atraumatic microvascular clamp [14]. After 30min of hepatic ischemia, the clamp was removed and the abdomen was closed. Then the rats were kept in clean cages during postoperative period. After 4h of reperfusion, animals were euthanized for blood and tissue collection.

Thirty-two rats were randomized into four groups (n=8):

Group S: Only portal vein and hepatic artery exposure was performed and 5ml/kg normal saline (NS) was given.

Group IRI: 5ml/kg NS was given intraperitoneally 30min before hepatic ischemia, after 30min of ischemia, the reperfusion was initiated.

Group D10: 10μg/kg (2μg/ml) dexmedetomidine was given intraperitoneally 30min before hepatic ischemia, after 30min of ischemia, the reperfusion was initiated.

Group D100: 100μg/kg (20μg/ml) dexmedetomidine was given intraperitoneally 30min before hepatic ischemia, after 30min of ischemia, the reperfusion was initiated.

2.4. Samples Collection

Blood samples were collected from inferior vena cava, and serum was obtained after blood centrifugation, and then frozen at -80°C for further analysis. Liver tissues were removed by washing with saline, and were frozen at -80°C for biochemical analysis. In addition, liver tissues taken for histopathological evaluation were fixed in 10% formaldehyde solution.

2.5. Biochemical Analysis

2.5.1. Evaluation of Liver Function

Serum levels of total bilirubin (TBIL), direct bilirubin (DBIL), aspertate transaminase (AST) and alanine transaminase (ALT) were measured using a serum multiple analyzer (Hitachi Ltd., Tokyo, Japan).

2.5.2. Evaluation of Inflammatory Response and Oxidative Stress

Systemic inflammatory response was reflected by serum level of TNF-α tested by commercial ELISA kits (Nanjing Jiancheng Biologic Product, China) according to the manufacturer's procedure. Oxidative stress was indicated by SOD activity and MDA level in liver tissues. Tissues were homogenized on ice with normal saline, frozen in a refrigerator at -20°C for 5 min and centrifuged, supernatants were collected for evaluation. SOD activity and MDA level were measured using commercially available WST-1 assay kits and TBA assay kits (Nanjing Jiancheng Biologic Product,

China), respectively.

2.6. Histopathological Investigations

Formalin-fixed tissues were embedded in paraffin wax, cut into 4 μm sections and stained with haematoxylin and eosin (HE) and Masson's trichrom. All tissues were examined with microscope for histopathological assessment.

2.7. Statistic Analysis

Statistical analysis was performed using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation (SD) values. Groups were compared using one-way ANOVA or nonparametric Kruskal-Wallis test (Equal variance not assumed). Values of $P < 0.05$ were considered statistically significant.

3. Results

3.1. Rat Model of Cholestasis and Liver Fibrosis

To confirm the establishment of cholestasis and liver fibrosis rat model, 6 rats undergoing BDL for 18d were compared with another 6 rats without BDL as control by TBIL, DBIL, liver morphological and histopathological changes. BDL rats showed enlarged yellow livers and elevated bilirubin level (Figure 1, Table 1). Microscopic sections of BDL livers showed inflammatory reaction, hepatocytes swelling, disordered arrangement of hepatic sinusoids, ductular proliferation and liver fibrosis (arrow) (Figure 2, Figure 3).

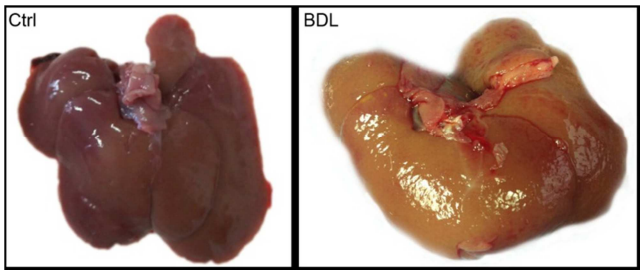

Figure 1. *Comparison of liver morphological changes after BDL: Livers in control group were grossly normal, exhibited normal structure, color and smooth surface. In contrast, livers with BDL were enlarged, cholestatic and with rough surface.*

Table 1. *Comparison of bilirubin levels after BDL ($\bar{x} \pm s$, n=6).*

Groups	TBIL (μmol/L)	DBIL (μmol/L)
Control	1.00±0.24	0.53±0.38
BDL	103.98±17.20[a]	59.43±18.17[b]

[a] compared with Control Group ($P \leq 0.000$).
[b] compared with Control Group ($P \leq 0.000$).

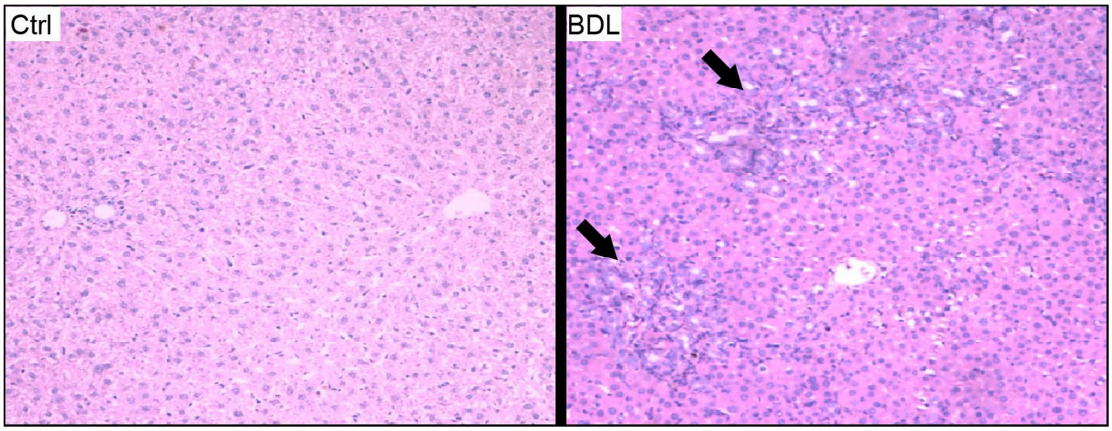

Figure 2. *Histopathological changes in HE staining (200×): Livers in control group showed normal structures with distinct central veins and portal triad. Livers with BDL showed inflammatory cells infiltration, disarranged hepatic sinusoids and ductular proliferation (arrow).*

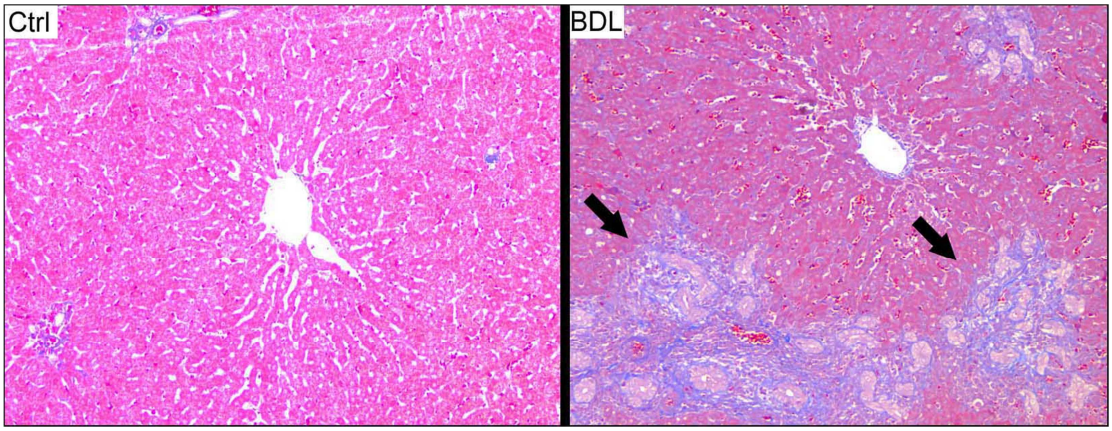

Figure 3. *Histopathological changes in Masson's trichrome staining (200×): Livers in control group showed little collagen deposited (blue stained) around portal triad. Livers with BDL showed large areas of fibrotic tissues (blue stained) in liver parenchyma (arrow).*

3.2. Hepatic Ischemia Reperfusion Injury

3.2.1. Comparison of Serum Bilirubin Levels

TBIL and DBIL values were dramatically elevated in all of the rats, but there were no significant differences between four groups (Table 2).

Table 2. *Comparison of serum TBIL and DBIL levels in four groups ($\bar{x} \pm s$, n=8).*

	S	IRI	D10	D100
TBIL (μmol/L)	111.05±24.23	102.14±18.05	99.80±16.23	117.23±17.30
DBIL (μmol/L)	77.09±26.60	57.80±26.72	68.31±18.62	78.15±29.42

Groups are as follows: S = Sham, IRI = Ischemia Reperfusion Injury, D10 = Dexmedetomidine 10μg/kg, D100 = Dexmedetomidine 100μg/kg.

3.2.2. Comparison of Serum Aminotransferase Levels

AST in group IRI, D10 and D100 were significantly higher than in group S, AST in D10 and D100 were both lower than in IRI, AST in D100 is significantly lower than in group D10. ALT in group IRI was significantly higher than in group S, ALT in group D100 was significantly lower than in Group IRI (Table 3).

Table 3. *Comparison of serum AST and ALT levels in four groups ($\bar{x} \pm s$, n=8).*

	S	IRI	D10	D100
AST (μmol/L)	454.15±118.08	1271.22±117.26[a]	847.27±198.64[ac]	621.83±102.49[bcd]
ALT (μmol/L)	125.34±36.40	285.31±167.69[e]	222.15±100.04	176.08±65.94[f]

Groups are as follows: S = Sham, IRI = Ischemia Reperfusion Injury, D10 = Dexmedetomidine 10μg/kg, D100 = Dexmedetomidine 100μg/kg.
[a] Compared with S group ($P \leq 0.000$).
[b] Compared with S group ($P \leq 0.023$).
[c] Compared with IRI group ($P \leq 0.000$).
[d] Compared with D10 group ($P \leq 0.003$).
[e] Compared with S group ($P \leq 0.005$).
[f] Compared with IRI group ($P \leq 0.046$).

3.2.3. Comparison of Serum TNF-α Levels

TNF-α in group IRI, D10 and D100 were significantly higher than in S, TNF-α in D10 and D100 were both significantly lower than in IRI (Table 4).

Table 4. *Comparison of serum TNF-α levels in four groups ($\bar{x} \pm s$, n=8).*

	S	IRI	D10	D100
TNF-α (pg/mL)	35.93±2.40	60.22±5.20[a]	47.36±4.54[ab]	45.06±4.64[ab]

Groups are as follows: S = Sham, IRI = Ischemia Reperfusion Injury, D10 = Dexmedetomidine 10μg/kg, D100 = Dexmedetomidine 100μg/kg.
[a] Compared with S group ($P \leq 0.000$).
[b] Compared with S group ($P \leq 0.000$).

3.2.4. Comparison of SOD Activities and MDA Levels in Liver Tissues

SOD in group IRI, D10 and D100 were significantly lower than in S, but SOD in D10 and D100 were both significantly higher than in IRI. MDA in group IRI, D10 and D100 were significantly higher than in Group S, but MDA in D10 and D100 were both significantly lower than in IRI (Table 5).

Table 5. *Comparison of SOD activities and MDA levels of liver tissues ($\bar{x} \pm s$, n=8).*

	S	IRI	D10	D100
SOD（U/mgprot）	102.84±16.18	41.03±6.95[a]	71.05±6.82[ab]	74.49±8.37[ab]
MDA（U/mgprot）	0.77±0.24	2.37±0.64[a]	1.57±0.57[ce]	1.41±0.45[df]

Groups are as follows: S = Sham, IRI = Ischemia Reperfusion Injury, D10 = Dexmedetomidine 10μg/kg, D100 = Dexmedetomidine 100μg/kg.
[a] Compared with S group ($P \leq 0.000$).
b Compared with IRI group ($P \leq 0.000$).
[c] Compared with S group ($P \leq 0.003$).
[d] Compared with S group ($P \leq 0.014$).
[e] Compared with IRI group ($P \leq 0.004$).
[f] Compared with IRI group ($P \leq 0.001$).

3.2.5. Results of Histological Findings

Microscopic sections of livers in four groups showed similar histological changes of hepatocytes swelling, hepatic sinusoids disorder, ductular proliferation and liver fibrosis. Liver tissues in S group showed mild inflammation and lymphocytes

infiltration, while IRI group showed severe damages of liver tissues with a mount of lymphocytes, neutrophils and eosinophils infiltration, there were several necrotic areas in 5 out of 8 rat livers in IRI group. D10 and D100 group showed moderate injury with inflammatory cells infiltration (Figure 4).

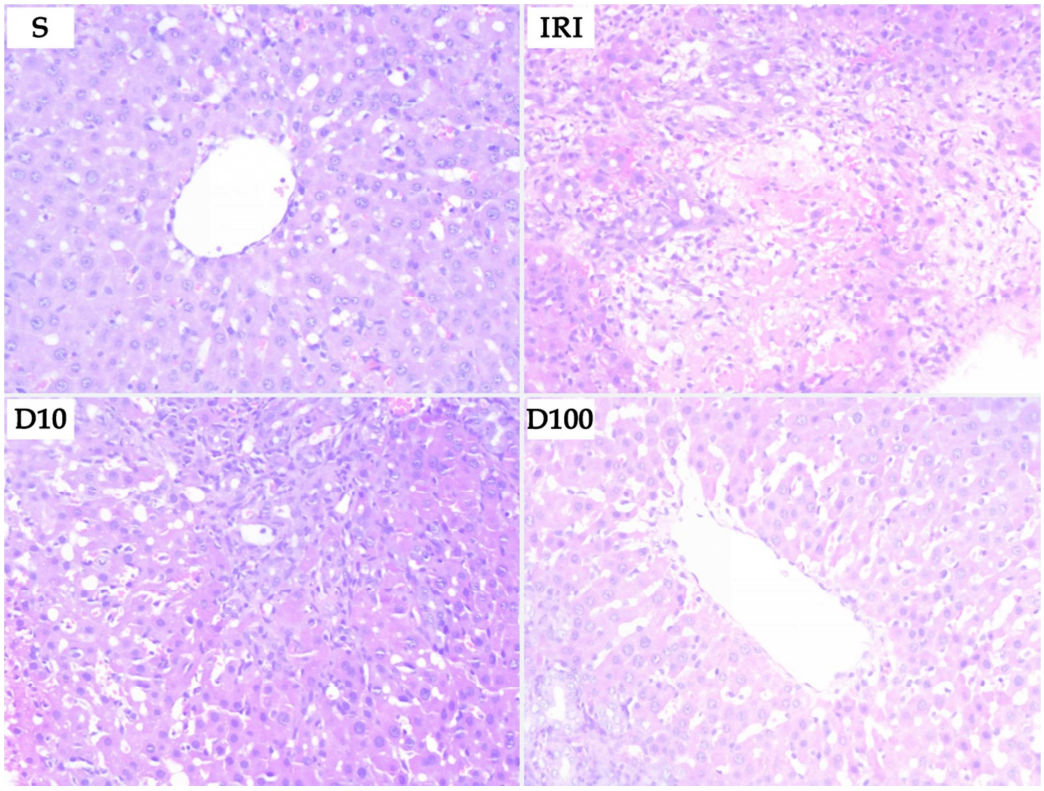

Figure 4. *Histopathological changes of livers in 4 groups (200×): Liver tissues in S group showed disarranged sinusoids and mild lymphocytes infiltration. IRI group showed severe damages of liver tissues with lymphocytes, neutrophils and eosinophils infiltration, necrotic areas were also detected. D10 and D100 group showed moderate injury with inflammatory cells infiltration.*

4. Discussion

The present study showed that dexmedetomidine may have the property to attenuate hepatic IRI in rats with cholestasis and liver fibrosis.

4.1. Ischemia Reperfusion Injury in Marginal Liver

Liver resection is an effective therapeutic management for hilar cholangiocarcinoma and hepatolithiasis, howerver, Pringle maneuver for reducing blood loss during hepatectomy inevitably causes hepatic IRI and impairs liver function [2-5]. Oxidative stress and inflammatory response play a key role in early stage of hepatic IRI. In normal liver, ROS is produced by oxidative phosphorylation from respiratory chain in mitochondria, and is kept balanced by oxidation reduction system. However, hepatic IRI may trigger excessive releasing of ROS from various sources in a short time, it breaks the oxidation/anti-oxidation balance, induces lipid peroxidation, DNA oxidation and enzymes degeneration of the hepatocytes [7]. Meanwhile, ROS could also act as a signaling molecule to up-regulate TNF-α expression and triggers massive inflammatory factors releasing from KCs, endothelial cells and hepatocytes, this inflammatory network aggravates liver damage during IRI [8].

Moreover, patients with hilar cholangiocarcinoma or hepatolithiasis may even be complicated with cholestasis and liver fibrosis, evidence showed that if cholestasis occurred, there appeared massive neutrophil accumulation, hepatocellular edema, and sinusoidal endothelial cells (SEC) dysfunction in the liver, these changes made liver susceptible to oxidative stress and inflammation[9]. Kloek et al. [16] revealed that cholestasis strongly decreased hepatic antioxidant capacity and increased lipid peroxidation in rats, it also resulted in severe hepatic necrosis and apoptosis. Besides, patients with liver fibrosis or cirrhosis were more likely to suffer hepatic failure after hepatectomy because of impaired liver function reserve [10, 17]. Therefore, to protect liver with cholestasis and fibrosis from IRI is extremely important.

4.2. Anti-Oxidation and Anti-Inflammation

Pharmacological preconditioning such as antioxidant and anti-inflammatory substances have been proved effective for attenuating hepatic IRI, but few of the drugs or chemicals were available during operation [18]. Dexmedetomidine is a highly selective α_2-AR agonist, and is widely used as an anesthetic adjuvant during operation [11]. Evidences showed that dexmedetomidine could protect multiple organs from IRI by anti-oxidation, anti-inflammation, anti-necrosis and anti-apoptosis, the α_2-AR activation seems to be the key role

in the mechanisms [12-14]. However, the effect of dexmedetomidine on hepatic IRI with existed cholestasis and liver fibrosis is still unclear to our knowledge.

The present study showed that, dexmedetomidine preconditioning could increase SOD activity and decrease MDA content in the marginal rat livers after IRI. SOD is a critical enzyme to clear ROS, it could dismutate O_2^- into H_2O_2 and facilitate catalase (CAT) to clear H_2O_2 by reduction reaction [7]. On the other hand, MDA is produced by unsaturated fatty acid oxidation, it indicates peroxidative damage of cells [19]. Therefore, increased SOD activity and decreased MDA content in the results indicates that dexmedetomidine enhanced anti-oxidative capacity and mitigated lipid peroxidation in the marginal livers. Consistently, the results of serum aminotransferase levels demonstrated that less hepatocytes were injured after dexmedetomidine preconditioning. Sahin et al [20]. investigated that intraperitoneal injection of dexmedetomidine in dose of 10μg/kg or 100μg/kg could protect normal rat liver from IRI by increasing SOD, glutathione peroxidase (GSH-Px), and CAT enzyme activities, their results showed that dexmedetomidine in dose of 100μg/kg seems to be more effective than in dose of 10μg/kg, however, there seems to be no significant differences between the two doses in the present study. Previous studies showed that cholestasis may down-regulate α-AR expression in rat liver, but α_1-AR or α_2-AR were not differentiated in the studies [21-22]. Hence, there could be a possibility that cholestasis may down-regulate α_2-AR expression or interfere the binding of α_2-AR with dexmedetomidine, and diminish the protective effect of large dose of dexmedetomidine.

Inflammatory factors such as TNF-α, IL-1 and IL-6 dramatically increased in the bloodstream during the early stage of hepatic IRI, TNF-α promotes adhesion molecules expression and stimulates chemokines, leading to neutrophils recruitment which release more ROS and creates further injury [7]. Moreover, TNF-α also up-regulates expression of pro-apoptotic proteins such as caspase-3, leading to apoptosis of hepatocytes and aggravates liver injury [8]. In the present study, serum TNF-α levels dramatically increased after IRI, histopathological results also showed severe infiltration of lymphocytes and neutrophils in sinusoids, however, minor damages were observed in rat livers which were preconditioned by dexmedetomidine. Besides, few further benefits were observed in large dose compared with low dose of dexmedetomidine preconditioning, this indicated that anti-inflammatory effect may be limited even increasing the dose of dexmedetomidine.

4.3. Limitations of the Study

This study has some certain limitations. Necrosis and apoptosis are important in hepatic IRI, protein measurements such as caspase-3 or Bcl-2 could be considered to further support the results. Pratap et al [23]. revealed that Hedgehog (Hh) signaling pathway might be a potential regulator of inflammation in the cholestatic liver, and Hh antagonist cyclopamine could protect liver from IRI in cholestatic rats. Therefore, further investigation could focus on the mechanism of protective effect of dexmedetomidine on hepatic IRI with cholestasis and fibrosis.

5. Conclusion

The results of this study indicated that bile duct ligation for 18 days could establish a rat model of cholestasis and liver fibrosis. dexmedetomidine preconditioning could attenuate hepatic IRI in rats with cholestasis and liver fibrosis, possibly by up-regulation of SOD activity and down-regulation of TNF-α expression, furthermore, protective effect of dexmedetomidine in a small dose may be comparable with a large dose. It provides an experimental evidence that patients with cholestasis and liver fibrosis may get benefits from dexmedetomidine during liver resection. However, dexmedetomidine is mainly metabolized by liver, it should be used cautiously in patients with impaired liver function.

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