American Journal of Medical Case Reports, 2024, Vol. 12, No. 3, 46-48
Available online at http://pubs.sciepub.com/ajmcr/12/3/5
Published by Science and Education Publishing
DOI:10.12691/ajmcr-12-3-5

Protective Effect of Dexmedetomidine Combined with Remote Ischemic Preconditioning on Hepatic Ischemia-reperfusion Injury: A Report on 16 Cases

Yongping Liu, Siyou Tan, Lai Wei, Wenyan Chen*

Department of Anesthesiology, Hunan Provincial People's Hospital
(The First Affiliated Hospital of Hunan Normal University), Changsha, China
*Corresponding author: 11023148@qq.com

Received February 12, 2024; Revised March 14, 2024; Accepted March 21, 2024

Abstract This study aimed to investigate the effect of dexmedetomidine (Dex) combined with remote ischemic preconditioning (RIPC) on hepatic ischemia-reperfusion injury (HIRI) in patients undergoing hepatectomy. This study was designed as a prospective trial including ASA I-III patients aged 18 to 65 years scheduled for elective laparoscopic hepatectomy. Patients were randomly divided into two groups with 8 cases in each group: control and Dex combined with RIPC (DR) group. Information was collected regarding gender, age, height, weight, portal triad clamping time, operation time, intraoperative infusion volume, blood loss, and urine volume. Venous blood was collected after reperfusion to detect serum IL-6, ALT, AST, and TBIL. No difference was found in baseline information among the two groups ($P > 0.05$). Among the two groups, the serum level of ALT and AST in group DR was significantly decreased compared with the controls ($p < 0.05$), and the differences in postoperative serum IL-6 and TBIL levels between the two groups were not statistically significant ($P > 0.05$). The study demonstrated that the combined use of Dex and RIPC could alleviate HIRI caused by blocking the hepatic portal during laparoscopic hepatectomy.

Keywords: *Hepatic Ischemia-reperfusion Injury, Dexmedetomidine, Remote Ischemic Preconditioning, Hepatectomy*

Cite This Article: Yongping Liu, Siyou Tan, Lai Wei, and Wenyan Chen, "Protective Effect of Dexmedetomidine Combined with Remote Ischemic Preconditioning on Hepatic Ischemia-reperfusion Injury: A Report on 16 Cases." *American Journal of Medical Case Reports*, vol. 12, no. 3 (2024): 46-48. doi: 10.12691/ajmcr-12-3-5.

1. Introduction

Hepatic lobectomy is a common surgical treatment for hepatic bile duct stones and tumors; however, during hepatic resection, surgeons often need to reduce blood flow into the liver by blocking the hepatic hilar, thereby reducing bleeding during liver resection. When the blockage is released, the restored blood perfusion of the liver tissue not only fails to restore its function but also undergoes a phenomenon of more severe tissue injury and dysfunction, i.e., hepatic ischemia/reperfusion injury (HIRI) [1]. HIRI is a common pathological process in hepatic surgical disorders such as the management of severe hepatic trauma, the performance of extensive hepatic resections, liver transplantation, etc. HIRI has been used to mitigate the effects of liver transplantation and to reduce bleeding during hepatic resection. Currently, the main methods used to mitigate HIRI at home and abroad include ischemic preconditioning (IPC), ischemic postconditioning (IPO), pharmacological interventions, and so on [2]. Among them, IPC has received wide attention because it can effectively simulate the pathophysiological process of tissue cells in ischemia hypoxia and blood flow reperfusion. researchers attempted to treat one side of the human upper limb with transient ischemia and found that this method could reduce endothelial cell dysfunction caused by ischemia-reperfusion injury, which led to the proposal of remote ischemic preconditioning (RIPC) [3]. Compared to IPC, RIPC is safe, noninvasive, and easy and feasible to administer, and its protective effects may be realized through interactions between neural, humoral, and systemic pathways.

Dexmedetomidine (Dex) is a sedative, analgesic, anxiolytic, and effective in decreasing myocardial oxygen consumption. As a novel and highly selective α2-adrenoceptor agonist, Dex is widely used in anesthesiology and ICU due to its significant clinical advantages and characteristics such as high safety, inhibition of sympathetic nervous system activity, stabilization of cardiovascular, and significant reduction of postoperative delirium and agitation without respiratory depression [4,5]. More and more attention has been paid to the anti-inflammatory actions of Dex. Earlier animal and clinical experiments reported the ability of Dex to reduce the levels of proinflammatory cytokines such as

TNF-α and IL-6, further attenuating inflammatory response in the acute phase, and decreasing HIRI-related mortality as well [6,7]. Such anti-inflammatory properties may relate to the dose, which was proved by Sezer et al. [8] who found that both moderate (i.e., 5μg/kg/h) and high (i.e., 10μg/kg/h) doses of Dex were able to lower TNF-α and IL-6 in septic rats, while low dose (i.e., 2.5μg/kg/h) had no obvious effect. Results from Huang et al. [9] concluded Dex could significantly reduce postoperative AST, ALT, IL-6, and MDA among patients undergoing hepatectomy, indicating that Dex could improve liver function by inhibiting the production of inflammatory factors. Animal studies have shown that Dex has significant anti-inflammatory effects and can effectively reduce the release of pro-inflammatory mediators including TNF-α, IL-6, IL-1β and inducible nitric oxide synthase (iNOS) in ischemia/reperfusion rats, and thus attenuates HIRI [10]. Currently, there are no domestic or international reports on the effects of dexmedetomidine combined with distal ischemic preconditioning on HIRI in humans.

2. Case Descriptions, Methods, and Materials

In this study, we prospectively enrolled 16 patients who underwent hepatic lobectomy to investigate the role of the combination of the two on HIRI in patients who underwent laparoscopic hepatic lobectomy by determining postoperative hepatic function and inflammatory factors. Patients were all male, from 18 to 65 years of age, and signed a consent form permitting the use of medical history and imaging for publication.

In each case, the patients were fasted for 8 hours and abstained from drinking for 2 hours. Intraoperative monitoring of invasive arterial blood pressure, heart rate, electrocardiogram, and oxygen saturation was performed. Standardized anesthesia protocol was used: midazolam 0.05 mg/kg, sufentanil 0.5ug/kg, propofol 1mg/kg, and cisatracurium benzenesulfonate 0.02 mg/kg for anesthesia induction. Anesthesia maintenance was performed by 1-2% sevoflurane inhalation, intravenous continuous pumping of remifentanil, propofol, cis-atracurium benzenesulfonate, and intraoperative additional sufentanil as needed. Intraoperatively, different types of vasoactive drugs were given according to the patient's vital sign values, so that the blood pressure and heart rate were maintained at the admission base value ± 20% to ensure circulatory stability. The nasal temperature was maintained at 36-37°C. Intraoperative hemoglobin <7.0 g/L was transfused.

The patients were divided into two groups, the Control group and the DR group. In the DR group, Dex (4 ug/ml) was pumped at a loading dose of 1 ug/kg for 15 min 10 min after tracheal intubation, followed by continuous intravenous pumping at a dose of 0.5 ug/ kg/h until the end of the operation. The tourniquet was pre-tied to the root of the thigh of the left lower limb, and 10 min after anesthesia intubation, the tourniquet was inflated with the pressure set at 200 mmHg (1 mmHg = 0.133 kPa) to make the left lower limb ischemic (the success criterion of ischemia: the dorsalis pedis arterial pulsation of the left lower limb could not be palpated), and the tourniquet was continuously inflated for 5 min, and then deflated to 0 mmHg to restore the blood flow of the lower limb, which lasted for 5 min; the above procedure was repeated three times for a total of 30 min. The above procedure was repeated 3 times for a total of 30 min. patients in the control group were injected with the same amount of 0.9% sodium chloride injection as that in the DR group, and the patients were tied with a tourniquet on the left lower limb thigh for 30 min without inflation and deflation.

The age, height, and weight of all patients; total intraoperative hepatic portal blockade time, operative time, blood loss, total fluid infusion, and urine output were recorded. After blood samples were collected. 3 ml of peripheral venous blood was collected 4 h after reperfusion, and enzyme-linked immunosorbent assay (ELISA) was applied to the collected blood specimens to determine the serum levels of ALT, AST, total bilirubin (TIBL), and IL-6. The data were statistically analyzed using SPSS 26.0 software. Normally distributed measurements were expressed as mean ± standard deviation ($\bar{x}\pm s$), and one-way ANOVA was used for comparison between groups, while those that did not conform to the normal distribution were expressed as median (M) and interquartile spacing (IQR); counting data were presented as cases (%) by using Fisher's exact probability and $\chi 2$ tests. and $\chi 2$ test. $p < 0.05$ was considered statistically significant.

3. Results

Table 1. Comparison of the characteristic data. ($\overline{X} \pm S$)

Items	Groups	
	Control group (n=8)	DR group (n=8)
Age (year)	51.80±8.22	51.10±10.82
Body mass index (kg/M²)	23.70±2.38	22.73±3.04
Blood occlusion (min)	47.50±3.72	47.70±3.77
Length of the surgery (min)	337.25±24.89	319.05±26.74
Fluid infusion (mL)	2252.50±150.85	2365.00±393.23
Bleeding (mL)	282.50±94.97	295.00±155.51
Urine volume (mL)	550.50±174.72	585.00±187.85

Table 2. Comparison of postoperative serum AST, ALT, TBIL, and IL-6 levels between the two groups of patients (n=8, per group , $\overline{X} \pm S$)

Groups	AST (U/L)	ALT (U/L)	TBIL (μmol/L)	IL-6 (ug/L)
Control group	310.20±12.30	205.94±12.17	19.79±1.21	2.22±0.71
DR group	86.73±3.46*	88.78±7.19*	18.00±2.34	1.52±0.68

*, Comparison with Control group, $P<0.05$.

There were no significant differences in age and body mass index between the two groups of patients (P > 0.05). Comparison of intraoperative data profiles between the two groups of patients in terms of hepatic portal block time, operative time, volume of fluid infusion, bleeding volume, and urine volume were not significantly different (P > 0.05) (Table 1). As shown in Table 2, the postoperative serum ALT and AST levels of patients in

the DR group were significantly lower than those in the Control group ($P < 0.05$); the differences in postoperative serum IL-6 and TBIL levels between the two groups were not statistically significant ($P > 0.05$).

4. Discussion

This study included patients with hepatolithiasis scheduled for laparoscopic left hepatolobectomy and observed the effect of combined use of Dex and RIPC on hepatocyte integrity markers (i.e., AST and ALT) and inflammatory marker (IL-6) among patients with HIRI hepatic portal occlusion. We found that the serum level of ALT and AST in group DR was significantly decreased compared with the controls, pointing out that Dex and RIPC could effectively attenuate the hepatocellular damage. No statistical differences in IL-6 and TBIL between group DR and the control group. In a recent study, it has been demonstrated in animals that RIPC significantly reduced the levels of intrinsic liver enzymes, IL-6, and TNF-α in a mouse model of HIRI, and this effect might be mediated through the HMGB1/TLR4/NF-κB pathway [11]. There are some limitations to this study. First, this study was limited to patients with hepatolithiasis, thus the effective protective effect of Dex and RIPC on other liver diseases with hepatolobectomy required further research. Second, although we confirmed the test dose of Dex and ischemic time and the cycle of RIPC concerning the current status of clinical application, the intervention regimen remained more evidence and clinical observations regarding the dose-response response of Dex and appropriate RIPC when the two are used in combination. Third, only transaminases and inflammatory markers (IL-6) were used for assessment, other indicators for evaluation on liver damage, oxidative stress levels, and inflammatory immune response are still needed to be validated in the future. Meanwhile, due to the limited sample size included, an expanded trial population or multiple centers are needed to validate the results reported in this case.

Overall, this study found that the strategy of combining Dex and RIPC had the effect of attenuating HIRI and protecting liver function in patients undergoing hepatic lobectomy, and this effect may be associated with improved liver function and alleviated cell injury.

Funding

This work was supported by the Health Commission of Hunan Province under Grant C2019049

References

[1] Mao B, Yuan W, Wu F, et al. Autophagy in hepatic ischemia-reperfusion injury [J]. Cell Death Discov, 2023, 9(1): 115.

[2] Osman AS, Osman AH, Kamel MM. Study of the protective effect of ischemic and pharmacological preconditioning on hepatic ischemic reperfusion injury induced in rats [J]. JGH Open, 2017, 1(3): 105-111.

[3] Rakic M, Patrlj L, Amic F, et al. Comparison of hepatoprotective effect from ischemia-reperfusion injury of remote ischemic preconditioning of the liver vs local ischemic preconditioning of the liver during human liver resections [J]. Int J Surg, 2018, 54(Pt A): 248-253.

[4] Baumgartner K, Doering, Mullins ME, et al. Dexmedetomidine in the treatment of toxicologic conditions: a systematic review and review of the toxicology investigators consortium database [J]. Clin Toxicol (Phila), 2022, 60(12): 1356-1375.

[5] Di Franco C, Evangelista F, Briganti A. Multiple uses of dexmedetomidine in small animals: a mini review [J]. Front Vet Sci, 2023, 10: 1135124.

[6] Kucuk A, Yaylak F, Cavunt-Bayraktar A, et al. The protective effects of dexmedetomidine on hepatic ischemia reperfusion injury [J]. Bratisl Lek Listy, 2014, 115(11): 680-4.

[7] Zhang S, Tang J, Sun C, et al. Dexmedetomidine attenuates hepatic ischemia-reperfusion injury-induced apoptosis via reducing oxidative stress and endoplasmic reticulum stress [J]. Int Immunopharmacol, 2023, 117: 109959.

[8] Sezer A, Memis D, Usta U, et al. The effect of dexmedetomidine on liver histopathology in a rat sepsis model: an experimental pilot study [J]. Ulus Travma Acil Cerrahi Derg, 2010, 16(2): 108-12.

[9] Huang YQ, Wen RT, Li XT, et al. The Protective Effect of Dexmedetomidine Against Ischemia-Reperfusion Injury after Hepatectomy: A Meta-Analysis of Randomized Controlled Trials [J]. Front Pharmacol, 2021, 12: 747911.

[10] Lee JE, Jung H, Byun SH, et al. Effect of Dexmedetomidine Preconditioning on Hepatic Ischemia-Reperfusion Injury in Acute Hyperglycemic Rats [J]. Transplant Proc, 2023, 55(10): 2478-2486.

[11] Koh WU, Kim J, Lee J, et al. Remote Ischemic Preconditioning and Diazoxide Protect from Hepatic Ischemic Reperfusion Injury by Inhibiting HMGB1-Induced TLR4/MyD88/NF-kappaB Signaling [J]. Int J Mol Sci, 2019, 20(23).