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Study on the protective mechanism of dexmedetomidine on the liver of perioperative diabetic patients

A randomized controlled trial

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Abstract

Background: Although several studies have reported that dexmedetomidine is a highly selective α2-adrenergic receptor agonist that protects liver function in perioperative patients by inhibiting oxidative stress (OS) and inflammatory response, patients with type 2 diabetes mellitus (T2DM) have not been included in the previous studies. The purpose of this study was to investigate the effects of perioperative low-dose dexmedetomidine on perioperative liver function in T2DM patients.

Methods: This was a single-center, placebo-controlled randomized trial. Fifty-four T2DM patients scheduled for debridement of lower extremity ulcers were included in this study and randomly divided into 2 groups (n = 27 per group): the dexmedetomidine group (DEX group) and the control group (CON group). Continuous intravenous infusion of dexmedetomidine (DEX group) or normal saline (CON group) was administered from the completion of monitoring to the end of surgery. All participants received femoral and sciatic nerve block with 0.33% ropivacaine. The main result was the activity of liver enzymes (AST, ALT) reflecting liver function. The secondary results included variables reflecting blood glucose (Glu), blood lipids (TG, HDL, LDL, total cholesterol), biomarkers of OS (MDA, SOD), and systemic inflammatory response (TNF-α, IL-6).

Results: Compared with CON group, DEX group exhibited a reduction in hemodynamic parameters, Glu, systemic inflammatory response, and liver injury indicators. OS response MDA activity was lower in DEX group than in CON group, while SOD was higher than that in CON group. The variables reflecting lipid metabolism function showed no differences between the groups.

Conclusion subsections: Dexmedetomidine administered perioperatively can reduce Glu levels and protect the liver by attenuating OS injury and inflammatory response in T2DM patients without any potential risk.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CON = control, DEX = dexmedetomidine, Glu = blood glucose, HDL = high-density lipoprotein, IL-6 = interleukin-6, LDL = low-density lipoprotein, MDA = malondialdehyde, NAFLD = nonalcoholic fatty liver disease, OS = oxidative stress, SOD = superoxide dismutase, T2DM = type 2 diabetes mellitus, TG = triglyceride, TNF-α = tumor necrosis factor-α.

Keywords: dexmedetomidine, liver function, nonalcoholic fatty liver disease, perioperative period, type 2 diabetes mellitus

1. Introduction

In 2010, approximately 285 million people worldwide had diabetes, 90% of whom had type 2 diabetes mellitus (T2DM). It is estimated that by 2030, the number of people with diabetes worldwide will increase to 439 million.[1] The prevalence of nonalcoholic fatty liver disease (NAFLD) is 25% worldwide, and 60% to 75% in patients with T2DM.[2,3] T2DM increases the risk of nonalcoholic steatohepatitis (NASH) (NAFLD with inflammation and hepatocellular damage, with or without fibrosis) by 2 times.[4] NASH can develop into cirrhosis, liver failure, hepatocellular carcinoma, and increase cardiovascular risk.[5,6] At present, the pathogenesis of NAFLD is multifactorial and complex, In recent years, studies have mostly proposed the "two-hit" hypothesis,[7] that is, after the first hit by the accumulation of fatty acids/triglycerides in the liver and the progression of insulin resistance,[8] the liver continues to be damaged by other factors, especially oxidative stress (OS) and systemic

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inflammatory response.[9] Surgery is an acute event, which not only results in localized tissue damage but also leads to systemic dysfunction. OS injury and inflammation are 2 important components in this process, and reactive oxygen species (ROS) play an important role in their modulation.[10] The production of ROS is enhanced in both diabetic humans and the animal models of the disease.[11,12] Clinically, the more extensive the surgical wound and tissue dissection, the greater are the OS response and inflammation.[13] Therefore, in the perioperative period, the operation may cause damage to liver function due to OS injury and the release of inflammatory factors, especially in T2DM patients. To date, NAFLD management is mainly focused on lifestyle through exercise and diet to achieve weight loss, which can reduce the potential cardiovascular and metabolic risks.[14–16] Anesthesiologists have the responsibility to optimize the long-term health and well-being of patients. If we can find drugs that can reduce the perioperative OS response and the release of inflammatory factors, liver function tests may be improved, while NAFLD progression may be inhibited. Therefore, inhibition of OS and inflammatory response during surgery is recognized as a potential therapeutic strategy for T2DM patients.

Dexmedetomidine is a highly selective alpha-2 adrenergic agonist, which is commonly used as an auxiliary sedative in clinical anesthesia. It has recently been reported that dexmedetomidine can reduce endoplasmic reticulum stress,[17] prevent sepsis, lessen histological damage, and diminish OS injury in animal models[18–20] to reduce hepatic ischemia-reperfusion injury. In addition, studies have shown that by inhibiting stress response, dexmedetomidine can maintain postoperative glucose stability and reduce Glu levels in patients with diabetes.[21] In recent years, clinical studies have found that perioperative use of dexmedetomidine can protect the liver by attenuating OS injury and inflammatory response in patients undergoing elective hepatectomy,[22] and also exerts protective effects against hepatic ischemia-reperfusion injury during adult living donor liver transplantation.[23] All of these indicate that dexmedetomidine may have a protective effect on liver function. In our previous research, we found that dexmedetomidine can protect liver cells by inhibiting OS response, attenuating inflammatory response, and regulating lipid metabolism in a high-fat diabetic hepatocyte model. However, in the perioperative period of T2DM patients, whether it can protect the organs, especially the liver, remains unclear.

In this randomized trial, we observed the effects of dexmedetomidine on hepatic function in T2DM patients undergoing debridement of lower extremity ulcers. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity, which were sensitive markers for the detection of liver function as we described before, were taken as the primary endpoint. Meanwhile, the biomarkers of OS, lipid metabolism, and systemic inflammatory response in serum were determined.

2. Methods and Materials

2.1. Ethics and informed consent

This study was approved by the Ethics Committee of Clinical Medical College and The First Affiliated Hospital of Chengdu Medical College (2020CYFYHEC-BA-64). The study obtained written informed consent were obtained from all participants. The study was registered in the Chinese Clinical Trial Registry (ChiCTR2000033428).

2.2. Participants and study design

This was a randomized, double-blind, single-center, parallel-controlled clinical trial. A total of 60 T2DM patients who were scheduled for debridement of lower extremity ulcers were enrolled in this study from June 1, 2020 to March 31, 2022, at The First Affiliated Hospital of Chengdu Medical College. Fifty-four eligible participants were included in the final analysis. They were randomly divided into the dexmedetomidine group (DEX group) and the control group (CON group), with 27 patients per group (Fig. 1). Inclusion criteria: Patients aged between 40 and 80 years old were diagnosed with T2DM (the diagnosis of T2DM is based on the 1999 World Health Organization criteria),[24] with American Society of Anesthesiologists (ASA) grade II or III. Exclusion criteria:

1. Those with significant arrhythmias, kidney dysfunction, pulmonary disease, and any other diseases or pathological conditions that can interfere with the experimental results.
2. Those with a history of drug abuse.
3. Those with a history of psychological disorders or psychotropic medication.
4. Those with a history of respiratory insufficiency or sleep apnea.
5. Those with diabetic ketoacidosis.
6. Those with contraindications to the use of dexmedetomidine such as allergy and atrioventricular block.

Termination criteria:

(1) The subjects refused to participate in the study midway;
(2) Intraoperative hemorrhage;
(3) Subjects with adverse events (such as drug allergy, severe bradycardia, anesthesia accidents, and surgical accidents);
(4) Change the way of operation and anesthesia.

On the day of surgery, the enrolled patients were randomly divided into DEX group or CON group by a single investigator who was involved only in randomization, using the random number table method. A random sequence without stratification was generated by a computer and sealed with consecutively numbered envelopes to conceal the random assignment. Before the operation, an independent anesthesiologist not involved in the study was responsible for preparing dexmedetomidine or saline placebo opened the envelope to show the allocation of treatment, and then used the same 50 ml syringe to extract the drug. Either 0.9% isotonic saline (CON group) or dexmedetomidine (DEX group) was diluted in 0.9% isotonic saline to a final volume of 50 mL (final concentrations: dexmedetomidine 4 μg/mL). We pumped the drug into the patient in a blind manner. Patients, surgeons, researchers, and statisticians were not aware of the blind assignment until the final statistical analysis was completed.

2.3. Anesthetic protocol

Monitoring was performed throughout the operation, and after entering the operating room, 5-lead electrocardiography, blood pressure, pulse, body temperature, pulse oxygen saturation, respiration, and other vital signs were monitored. Oxygen was delivered by a face mask. Intravenous channels were established, and lactate Ringer's solution was infused at 5 mL/kg/h. All patients underwent ultrasound-guided single-shot peripheral blocks of the femoral and sciatic nerves with 0.33% ropivacaine after venous access was established. All nerve blocks were created by a single anesthesiologist with extensive anesthetic experience in over 3000 cases. In DEX group, dexmedetomidine loading volume (0.5 μg/kg) was infused intravenously for 10 minutes after complete monitoring, and then 0.4 μg/kg/h continued to be pumped until the end of the operation. In CON group, patients were pumped with the same dose of normal saline in the same way. The doses selected were based on previous research and clinical experience of perioperative use of dexmedetomidine.[25–27]

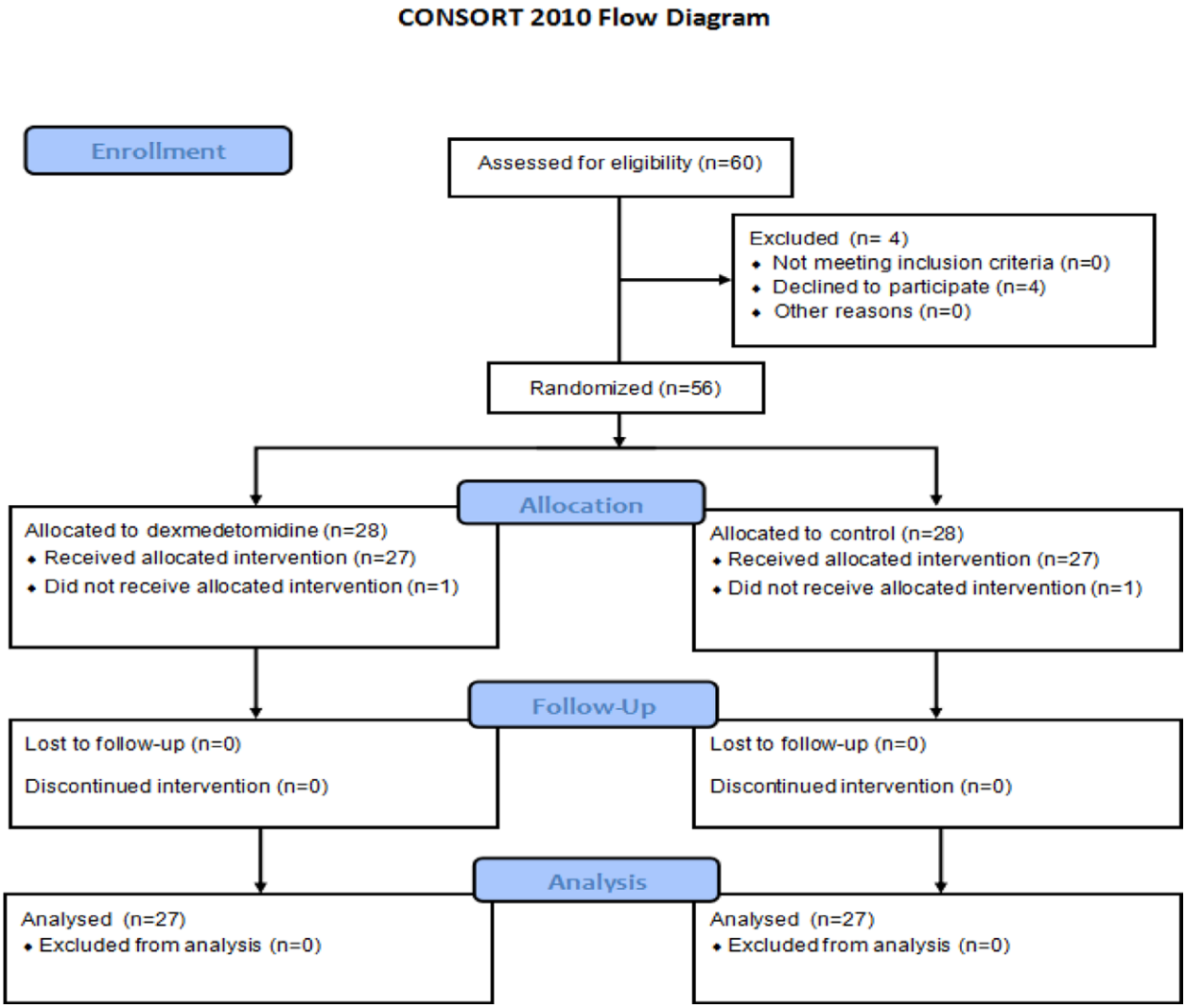

Figure 1. Consort diagram. Initially, 60 patients were randomly assigned to 1 of 2 groups as follows: the dexmedetomidine group (DEX group) or the control group (CON group). 54 patients (27 in DEX group and 27 in CON group) completed this study.

2.4. Blood samples collection and time points

Venous blood (2-3 mL) of patients was collected from peripheral veins at 5 different time points: before anesthesia (baseline, T0), at the end of surgery (T1), 1 day post-operation (T2), 3 days post-operation (T3), and 5 days post-operation (T4), followed by centrifugation at room temperature at 3000 r/minutes for 10minutes. The supernatant was isolated and stored at −80°C for further analysis.

2.5. Evaluation of liver function and lipid metabolism indicators

Liver function was assessed by ALT and AST activity, and lipid metabolism was evaluated by triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol levels at predetermined time points. These tests were carried out in the laboratory department of Shifang people's Hospital.

2.6. Evaluation of oxidative stress and inflammatory response

As mentioned above, the level of OS was reflected by serum malondialdehyde (MDA) and superoxide dismutase (SOD), and the level of inflammatory response was indicated by tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), using enzyme-linked immunosorbent assay (ELISA) following manufacturers instructions.

2.7. Adverse reactions

Adverse reactions, such as hypertension (MAP > 100 mm Hg), hypotension (MAP < 60 mm Hg), bradycardia (HR < 60 times/minutes) and tachycardia (HR > 100 times/minutes) were recorded during the perioperative period. Besides, the occurrence of nausea and vomiting after surgery was also recorded.

2.8. Statistical analysis

According to the pre-experimental results, the sample size calculation was based on the peak ALT concentration at 1 day after resection of the ulcer debridement as the primary outcome. Set intergroup effect δ=6.48IU/L, the standard deviation σ=6.98IU/L, with α=0.05 and power=0.8 was used to determine the study. According to the formula $N = 2 \times \left[\frac{(Z_{1-\alpha/2}+Z_{1-\beta})\sigma}{\delta}\right]^2$, estimate the effective sample size $N \approx 20$ for each group. Invasive clinical trials often need to recruit more subjects to prevent patients from falling out during follow-up. Based on experience,

it is assumed that 25% of the trials are lost to follow-up, so each group of samples is adjusted up to $N^{*}=N\div(1-0.25)\approx 27$.

Data analysis was achieved by using SPSS for Windows version 23.0. Normally distributed measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$). Continuous variables that were normally distributed were analyzed using an independent t-test, while non-normally distributed variables were analyzed using the Mann–Whitney *U* test for comparison between the groups. Repeated measures analysis of variance will be used for intra-group comparisons. The χ^2 test will be used for the comparison of count data. $P < .05$, indicating that the difference is statistically significant.

3. Results

3.1. Demographic and perioperative data

As shown in Table 1, there were no differences between the 2 groups in terms of gender, age, body mass index, ASA classification, duration of operation, duration of anesthesia, intraoperative blood loss, intraoperative infusion volume, Intraoperative local anesthetic volume, length of hospital stay, and the adverse reaction like nausea, vomiting, and bradycardia (all $P > .05$).

3.2. Hemodynamic data

From Figure 2A and B, MAP and HR were notably reduced after administration of dexmedetomidine ($P < .05$), but were then slowly enhanced at T2 compared with T1. In DEX group, the only significant changes compared with baseline (T0) were MAP and HR at T1 (all $P < .05$). At T1, the MAP and HR of DEX group were significantly lower than those of CON group ($P < .05$).

3.3. Blood glucose level

As displayed in Table Figure 2C, the Glu levels remarkably increased in CON group after the operation ($P < .05$), but was then slowly enhanced at T3 compared with T2, and reached a peak at T2 ($P < .05$), then recovered to baseline levels at T3. In DEX group, the Glu level increased at T2, T3, and T4 ($P < .05$).

Table 1

Demographic data in the study groups.

Index	CON group (n = 27)	DEX group (n = 27)	*P* value
Age (yrs)	63(55, 75)	57(53, 66)	.102
Body mass index (kg/m^2)	23.01 ± 3.07	24.45 ± 2.64	.071
Gender (Male/Female)	22/5	18/9	.447
ASA (II/III)	24/3	22/5	.444
Duration of surgery (min)	95.04 ± 36.23	76.81 ± 36.13	.070
Duration of anesthesia (min)	130(115, 135)	135(105, 155)	.298
Intraoperative blood loss (mL)	15(10, 20)	20(10, 40)	.093
Intraoperative 0.33% ropivacaine requirement (mL)	40(40, 40)	40(40, 40)	.844
Intraoperative 2% lidocaine requirement (mL)	0(0, 0)	0(0, 2)	.472
Intraoperative infusion volume (mL)	1000(500, 1000)	600(500, 1000)	.339
Length of hospital stay (d)	21(13, 35)	20(14, 31)	.473
Adverse reaction			
Nausea and vomiting [n (%)]	2 (7.4%)	3 (11.1%)	.639
Bradycardia [n (%)]	0 (0.00%)	1 (3.7%)	.313

Data are mean ± standard deviation.

ASA = American society of anesthesiology, CON = control group, DEX = dexmedetomidine group.

Compared with CON group, an obvious decrease in Glu levels in DEX group at T1 and T2 (both $P < .05$).

3.4. Analyses of OS and systemic inflammatory response

As shown in Figure 3A, the serum MDA levels increased to the peak at T1 ($P < .05$) and gradually returned to the baseline at T4 in CON group. In addition, MDA levels at T1, T2, and T3 in DEX group were lower than those in CON group (all $P < .05$). Figure 3B showed that SOD activity in CON group decreased after operation compared with T0 (all $P < .05$) and was higher in DEX group than that in CON group at T1 and T2 (all $P < .05$).

As shown in Figure 3C, TNF-a levels sharply peaked at T2 ($P < .05$) and gradually returned to the baseline at T3 in both groups and there were statistical differences between the groups at T1 and T2 (all $P < .05$). The IL-6 levels increased gradually and peaked at T2 and gradually returned to the baseline at T4 in both groups, and the levels in DEX group were lower than those in the control at T1, T2, and T3 (all $P < .05$) as shown in Figure 3D.

3.5. Analyses of liver function

Similarly, as shown in Figure 4A and B, there were no differences compared with T0 in terms of ALT and AST levels in both CON groups. ALT level remarkably decreased in DEX group after the operation ($P < .05$), and serum ALT and AST levels were lower in DEX group patients at T2 and T3 compared with CON group (all $P < .05$).

3.6. Analyses of blood lipids

All their values in both groups were normal at all time points and there were no differences between the groups as shown in Figure 5A–D.

4. Discussion

With the aging society and higher standard of living, people with T2DM have increasingly become the focus of attention. Diabetes and its associated complications seriously jeopardize human health. The longer the patient has type 2 diabetes, the more serious the damage to the body organs, especially the liver, which is one of the common complications of diabetes. Currently, NAFLD becomes an early complication that threatens patients with type 2 diabetes. The more obese the patient, the higher the prevalence of NAFLD, which is now the most common cause of chronic liver disease worldwide. Studies have shown that surgical incision and tissue manipulation lead to cell rupture releasing various intracellular chemical mediators, these pathophysiological changes may manifest as hyperalgesia, allodynia, and even persistent postoperative pain, and these responses to nociception contribute to the activation and potentiation of OS response associated with surgery,[28] and different surgical manipulations generate different levels of OS responses and inflammation.[29] Compared with ordinary patients, if the patient has type 2 diabetes or even fatty liver, then surgery will more easily aggravate the systemic OS, inflammatory factors release, lipid metabolism disorder, and even liver damage.[30] Without timely and effective intervention, it may increase the incidence of perioperative complications and even the risk of death. However, in addition to changing lifestyle and diet, there is still a lack of effective perioperative treatment measures. Although some drugs, such as oxygen radical scavengers, have been successfully used to preserve liver function in animal models, few of them can be used for severe adverse side effects in clinical

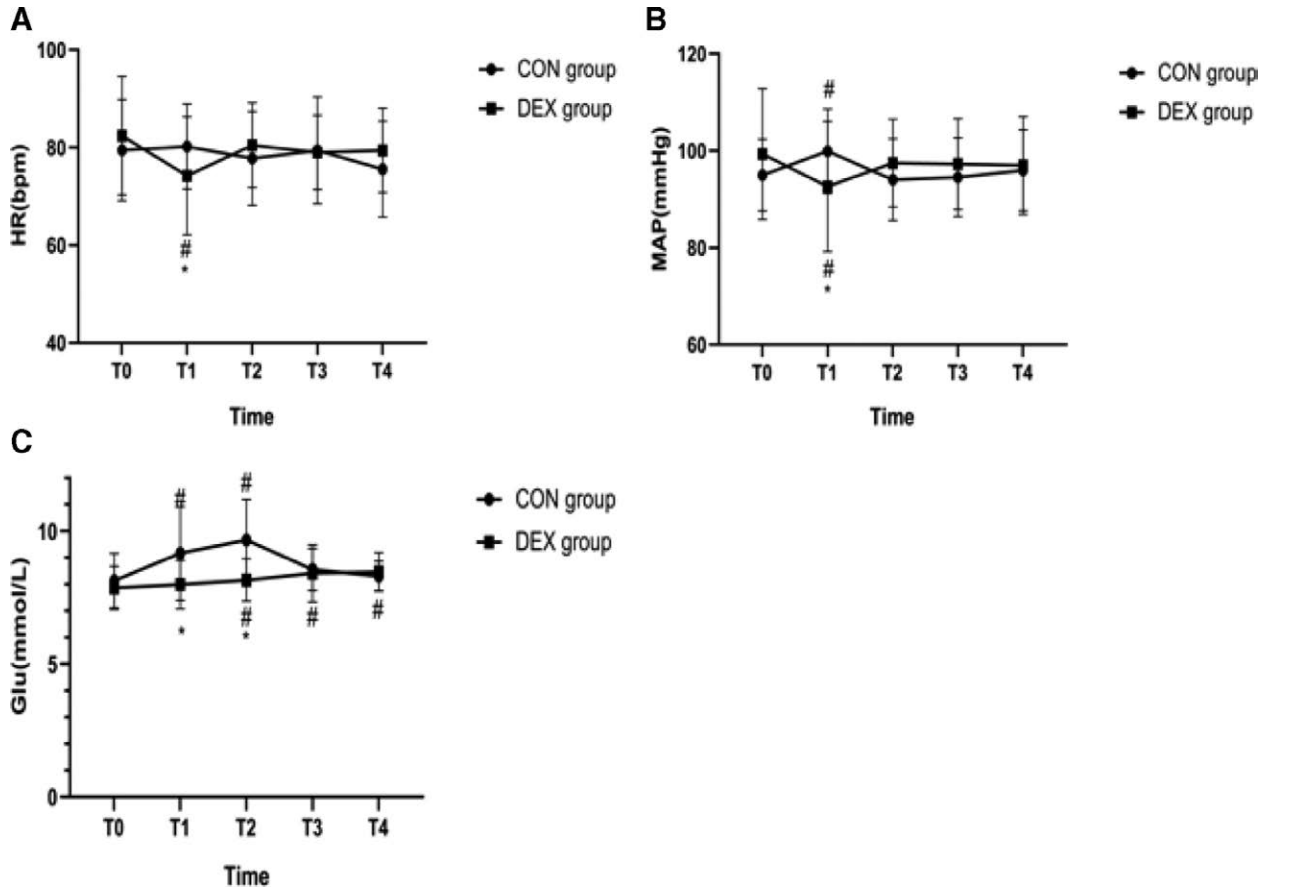

Figure 2. Variables reflecting hemodynamic data and blood glucose at various time points in patients with T2DM undergoing debridement of lower extremity ulcers with or without dexmedetomidine. n = 27 for each group. (A) Changes in the heart rate; (B) mean blood pressure; (C) blood glucose level. $^{\#}P < .05$ versus baseline; $^{*}P < .05$ versus control.

settings or may not be available during the surgical procedure.[31] Therefore, the effects of commonly used anesthetics or sedatives in anesthesia become more important to preserve liver function.

Reference to the relevant literature[32] and combined with clinical experience, excessive dexmedetomidine doses can cause transient hypotension and bradycardia. In this study, the dexmedetomidine loading capacity was set at 0.5 μg/kg and maintenance was 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ until the end of surgery. An increasing number of studies have shown[23,33–36] that dexmedetomidine, as an anesthetic adjunct, has a multi visceral protective effect, and has become more widely used in perioperative anesthetic management.[37,38]

4.1. The effect of dexmedetomidine on blood glucose levels in perioperative patients with T2DM

Dexmedetomidine is often used in the perioperative period, not only can it act on the central locus coeruleus α2 adrenergic receptor to inhibit stress and reduce hyperglycemia, it can also act on α2 adrenaline receptors acting on peripheral islet tissue cells to inhibit insulin secretion and increase Glu. However, the ultimate effect of dexmedetomidine on perioperative Glu levels is unclear. Studies have shown that the use of dexmedetomidine in pediatric cardiac surgery can suppress the stress response and significantly reduce Glu levels.[39] A study in healthy volunteers showed that dexmedetomidine could slightly increase Glu levels by inhibiting insulin secretion.[40] The results of this study found that the Glu levels in both groups were increased after the operation. Compared with the CON, the Glu levels of DEX group was significantly lower. Both surgery and pain can cause the body's stress response, which increases the secretion of stress hormones, reduces the body's sensitivity to insulin and the ability to absorb and utilize glucose for oxidative energy supply, resulting in increased Glu. The Glu levels was significantly increased, reflecting the changes of surgical stress on the body. The application of dexmedetomidine not only ensured stable intraoperative hemodynamics but also reduced postoperative Glu. Its analgesic effect or inhibition of stress response may play an important role. This indicates that the use of perioperative dexmedetomidine can better control the perioperative Glu level of T2DM patients.

4.2. The effect of dexmedetomidine on inflammatory factors in perioperative patients with T2DM

TNF-α and IL-6 are important inflammatory factors in the body and participate in the systemic inflammatory response. TNF-α is one of the pro-inflammatory cytokines that stimulate the acute phase responses; it is mainly produced by macrophages and monocytes, with multiple regulatory functions in the immune response, and is also a potential heat source. IL-6 is also known as Pro-inflammatory cytokines, secreted by T cells and macrophages to promote immune responses during infection and trauma, especially inflammation caused by burns or other tissue damage. In addition, TNF-α and IL-6 can also enhance the release of anti-inflammatory factors, such as soluble TNF-α receptor, which is typical anti-inflammatory factor among cytokines. This study showed that the concentrations of pro-inflammatory factors TNF-α and

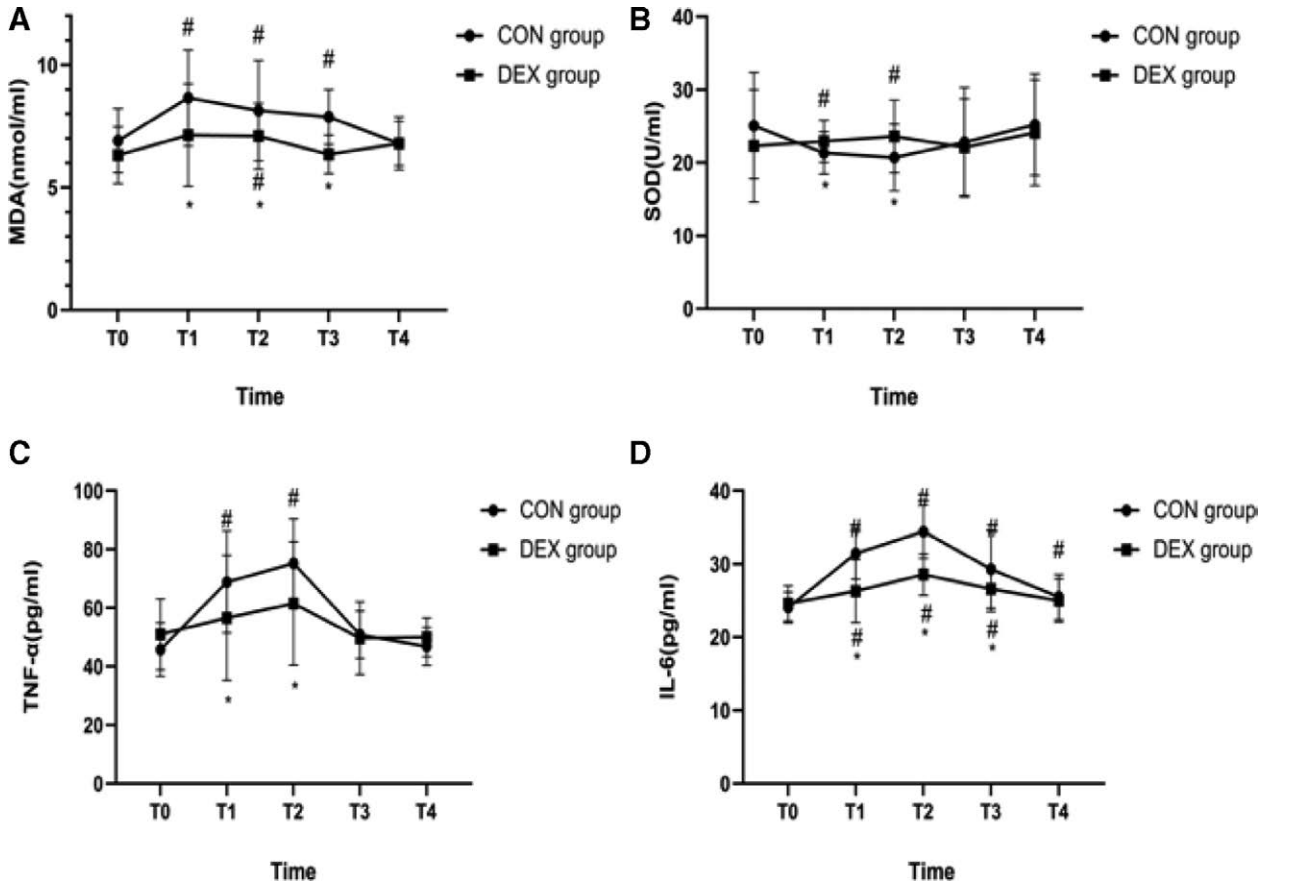

Figure 3. Variables reflecting oxidative stress and inflammatory response at various time points in patients with T2DM undergoing debridement of lower extremity ulcers with or without dexmedetomidine. n = 27 for each group. (A) Serum MDA concentration; (B) serum SOD activity; (C) serum TNF-a level; (D) serum IL-6 level. $^{\#}P < .05$ vs baseline; $^{*}P < .05$ vs control. IL-6 = interleukin-6, MDA = malondialdehyde, SOD = superoxide dismutase, T2DM = type 2 diabetes mellitus, TNF-α = tumor necrosis factor-α.

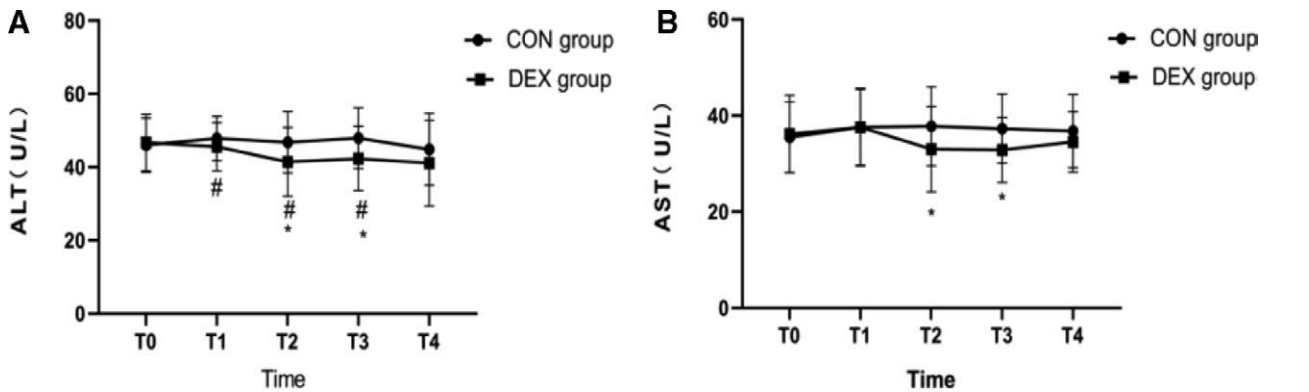

Figure 4. Variables reflecting liver function at various time points in patients with T2DM undergoing debridement of lower extremity ulcers with or without dexmedetomidine. n = 27 for each group. (A) serum ALT level; (B) serum AST level. $^{\#}P < .05$ versus baseline; $^{*}P < .05$ versus control. ALT = alanine aminotransferase, AST = aspartate aminotransferase, T2DM = type 2 diabetes mellitus.

IL-6 in DEX group were significantly lower than those in CON group, which directly proved that perioperative dexmedetomidine application in patients with type 2 diabetes can significantly reduce the inflammatory response.

4.3. The effect of dexmedetomidine on OS in perioperative patients with T2DM

The mechanisms of OS include excessive production of oxygen free radicals and disruption of the body's redox homeostasis. Clinically, electrocautery is used in most debridement operations for lower extremity ulcers to reduce intraoperative bleeding and it causes more ischemic tissue damage.[41] In this process, OS is one of the main manifestations of ischemia tissue injury. The production and release of a large number of oxygen free radicals lead to lipid peroxidation, resulting in damage to organ function. The level of MDA can reflect the degree of OS in tissue cells and the degree of damage to the body caused by lipid peroxidation.[42] SOD is the primary substance for scavenging oxygen free radicals and can maintain the body's oxidation

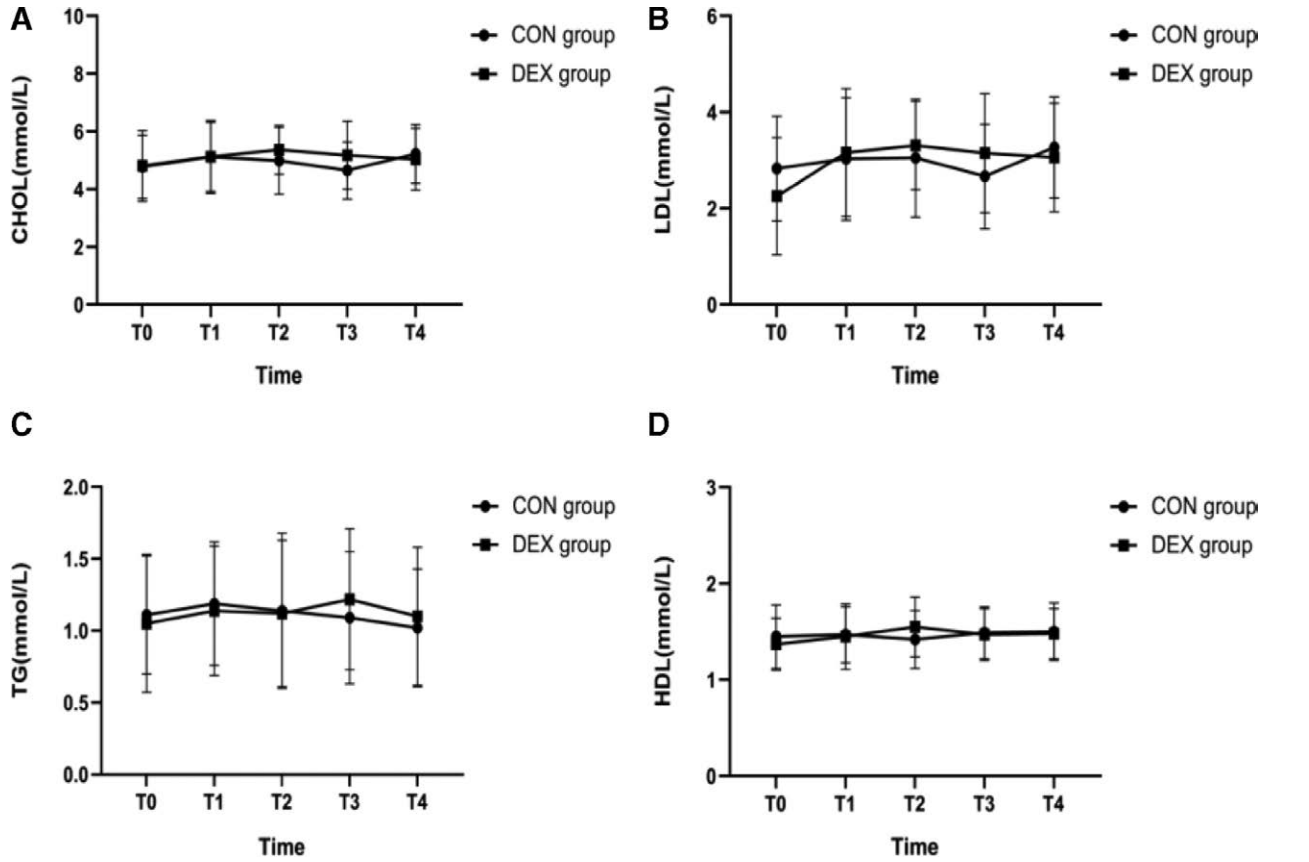

Figure 5. Variables reflecting blood lipid metabolism at various time points in patients with T2DM undergoing debridement of lower extremity ulcers with or without dexmedetomidine. n = 27 for each group. (A) serum CHOL level; (B) serum LDL level; (C) Serum TG level; (D) serum HDL level. $^{\#}P < .05$ versus baseline; $^{*}P < .05$ versus control. CHOL = total cholesterol. CHOL = total cholesterol, HDL = high-density lipoprotein, LDL = low-density lipoprotein, T2DM = type 2 diabetes mellitus, TG = triglyceride.

and antioxidant balance to protect cells from damage.[43–45] The detection of SOD activity can directly reflect the body's antioxidant capacity. Therefore, in this study, MDA and SOD were selected to represent the oxidative level and antioxidant capacity, respectively, to investigate the effect of dexmedetomidine on OS caused by debridement of the lower extremity in patients with T2DM. The results showed that the postoperative MDA concentration increased and the SOD concentration significantly decreased in CON group. It shows that the OS reaction occurs in the patient's body. The postoperative MDA concentration in DEX group is lower than that in CON group and the SOD concentration is higher than that in CON group. It was confirmed that dexmedetomidine has a protective effect on OS injury caused by debridement of lower extremity ulcers in patients with type 2 diabetes.

4.4. The effect of dexmedetomidine on the liver function of patients with T2DM in the perioperative period

Serum ALT and AST levels are sensitive indicators reflecting the degree of liver damage and can be used to assess liver function or liver damage. ALT and AST are mainly distributed in hepatocytes and a small fraction is present within the muscle cells. If the liver is damaged, transaminases in hepatocytes enter the blood and the levels of ALT and AST increase, signaling liver disease. Among them, ALT is the better sensitive transaminase and its activity in liver tissue is 100 times higher than that in serum. As long as 1% of liver cells are necrotic, ALT in serum can be doubled, while the continuous increase of AST level is a marker of the aggravation of chronic liver damage.[46–48] Therefore, in most cases, ALT and AST elevation are consistent with the degree of impaired liver function and are the most commonly used indicators of liver function detection. In this study, the postoperative transaminase indexes of the 2 groups of patients did not increase, indicating that, firstly, debridement of lower extremity ulcers and nerve block anesthesia will not cause damage to the body's liver function; Secondly, the perioperative small dose of dexmedetomidine pump does not cause liver function damage in patients with type 2 diabetes. It is also possible that the damage to liver function in the perioperative period is mainly due to the application of drugs metabolized by the liver. This type of surgery uses a simple nerve block instead of general anesthesia, which avoids the damage to the liver function of a variety of general anesthesia drugs. Compared with CON group, the ALT and AST levels in DEX group were significantly lower after the operation, which proved that dexmedetomidine has a protective effect on the liver function of patients with T2DM in the perioperative period.

4.5. The effect of dexmedetomidine on blood lipid metabolism in perioperative patients with T2DM

Body tissue steatosis is caused by the excessive deposition of lipids. In the human body, lipids mainly include 2 major categories: fats (mainly triglycerides) and lipids (cholesterol is an important one). Oxidation of triglycerides hydrolyzes to generate free fatty acids (FFA). The main function of HDL is to transport excess cholesterol in extrahepatic tissues to the liver for metabolism to prevent excessive accumulation of cholesterol in these tissues; LDL is a lipoprotein particle that carries cholesterol into peripheral tissue cells and is known as "bad cholesterol".[49–51]

Therefore, we detected the expression levels of lipid metabolism indicators such as triglyceride, total cholesterol, HDL, and LDL in each group. In this study, the expression levels of lipid metabolism indexes in the 2 groups of patients with type 2 diabetes after surgery were not found to be significantly different from the results of preoperative examinations. It showed that this dose of dexmedetomidine could not regulate the level of blood lipid metabolism in patients with T2DM undergoing such surgery. This was not consistent with the results of our previous basic research. Considering the reasons, it might be related to the dose and time of using dexmedetomidine.

The limitation of this study was that the number of samples was relatively limited under the influence of the epidemic, a large sample multicenter randomized controlled trial is still needed. Many factors were affecting the postoperative patient detection results during the study. we could not guarantee the principle of consistency, increased the error variation, and made it difficult to control the individual differences of subjects.

5. Conclusion

In conclusion, dexmedetomidine reduces the OS response and relieves inflammatory damage caused by lower limb ulcer debridement, and maintains Glu stability. Also, dexmedetomidine downregulates the expression of liver function markers, the mechanism may be due to the reduction of perioperative OS injury and the release of inflammatory factors. Dexmedetomidine does not increase perioperative adverse reactions, so dexmedetomidine can be safely used in clinical practice. However, the detailed mechanism of action is not clear, We still need a lot of experiments to study dexmedetomidine in the future.

Author contributions

Conceptualization: Lin Zeng.
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Funding acquisition: Shuhua Dong.
Investigation: Lin Zeng, Juan Liu, Lumiu Liao, Xuelian Chen.
Methodology: Juan Liu, Tianyao Zhang.
Project administration: Shuhua Dong.
Software: Tianyao Zhang.
Supervision: Shuhua Dong.
Validation: Shuhua Dong.

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