The Benefit of Dexmedetomidine on kidney are associated with the inhibition of oxidative stress during hyperthermic intraperitoneal chemotherapy: a randomized trail

YongHua Yao (yaoyonghua01@126.com)
Affiliated Cancer Hospital & Institute of Guangzhou Medical University

Xu Deng
The Second Affiliated Hospital of Guangzhou University of Chinese Medicine

RuiMin Luo
Foshan Hospital of Traditional Chinese Medicine

Yu Gu
Affiliated Cancer Hospital & Institute of Guangzhou Medical University

Research Article

Keywords: Dexmedetomidine, Hyperthermic Intraperitoneal Chemotherapy, Liver Function, Renal Function, Oxidative Stress

Posted Date: March 9th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1326124/v1

Abstract

Background: Hyperthermic intraperitoneal chemotherapy (HIPEC) may prolong the survival of patients with peritoneal carcinomatosis. The purpose of this study was to investigate whether dexmedetomidine protects liver and kidney function during HIPEC.

Methods: Sixty gastrointestinal cancer patients undergoing HIPEC were divided into two group. Patients in Dex group were received an intravenous infusion of dexmedetomidine until operation completed. The indexes about liver and kidney function and oxidative stress like malondialdehyde (MDA) and superoxide dismutase (SOD) were measured at different points.

Results: After HIPEC, these increases of renal damage markers were alleviated by Dex administration (P<0.05). Dex significantly alleviated the increased MDA concentration and decreased SOD activity caused by HIPEC (P<0.05). Dex also provide lower HR, bispectral index (BIS) and visual analogue scale (VAS), and more urine output(P<0.05).

Conclusion: Dex alleviated the impairment of renal function induced by HIPEC, which may be related to its better effects of analgesic, sedation and antioxidant.

1. Introduction

Gastrointestinal cancer (GI cancer) is a tumor that stem from the accessory organs of the alimentary tract, which account for half of the top 10 tumors with maximum mortality in the world, and more than 3 million patients die of it each year[1]. Peritoneal metastasis is the main cause of treatment failure for GI cancer, and also an important factor leading to cancer death. The incidence of peritoneal metastasis in postoperative recurrence of GI cancer can be up to 50% [2]. Despite multiple options, such as surgery, chemotherapy, radiotherapy and targeted therapy, have been adopted, the majority of patients suffering from cancer are prone to develop peritoneal recurrence and metastasis. Confirmed by previous studies, hyperthermic intraperitoneal chemotherapy (HIPEC) seems an effective therapy for preventing the peritoneal metastasis of GI cancer in clinical trials[3, 4]. HIPEC was combined with mechanical lavage, diathermy and local chemotherapy, which is expected to maximize eliminate free cancer cells and minimal residual lesions in the abdominal, thus, improving survival rates. Compared with systemic chemotherapy, HIPEC achieves antitumor effects with minimal general toxicity.

Some studies have shown that HIPEC induced cancer cell death is associated not only with hyperthermia and chemotherapy drugs, but more importantly with oxidative stress induced by hyperthermia exposure. Lehmann K et al. point out that induction of reactive oxygen species (ROS) generation during HIPEC is an appealing approach to kill residual cancer cells[5]. Excessive oxidative stress during surgery is known to cause tissue damage. Currently, the intensity of oxidative stress during HIPEC and whether it is associated with vital organs damage are not clear. Some reports have indicated that the incidence of renal insufficiency in patients undergoing cell reduction surgery (CRS)-HIPEC ranges from 2–22% [6]. And

a few cases of hepatic insufficiency and necrosis following HIPEC has been reported also[7]. Conducted a prospective study to identify the actual occurrence and related risk factors of liver and renal injury after HIPEC, and to clarify the relationship between oxidative stress and organs damage is necessary.

Dex is a sedative and analgesic drugs widely used in perioperative period, which is a highly selective a2 adrenoreceptor agonist[8]. Previous studies have demonstrated that Dex could protect against tissues injury by preventing oxidative stress[9]. Therefore, we speculated that administration of dexmetomidine during HIPEC may influence redox state in vivo, and further affect the function of renal and liver as well as patient prognosis.

2. Patients And Methods

2.1 *Participants*

All experimental protocols were approved by a ethics committee of guangzhou medical university and ethics licensing committee. This study was conducted at affiliated cancer hospital & institute of guangzhou medical University(23/12/2019), between July 2019 and November 2019 after registration at http://www.chictr.org.cn/ (ChiCTR1900026764)(21/10/2019) and written informed consent was obtained from all subjects and their legal guardians. All methods were carried out in accordance with relevant guidelines and regulations or Declaration of Helsinki.The participants were chose from patients with gastric and colorectal cancer undergoing HIPEC. After signed the informed consent, 60 patients (18–60 years old, American Society of Anesthesiologists /ASA I∼II) who received the third course of HIPEC were enrolled in the study.

Exclusion criterias: liver dysfunction, renal insufficiency, severe heart disease, history of drug abuse, neuropsychiatric disorders and allergy.

2.2 Study protocol

The patients were randomly and equally assigned into 2 groups using randomization list that generated by compute. The results of randomization were concealed in sequentially numbered opaque envelopes, which were opened by an anesthesiologist assistant who was prepared drugs and not involved in the study. All patients, investigators and personnel associated with this study were blinded to the assignment.

After entered the operating room, conventional monitoring such as electrocardiogram (ECG), NIBP, pulse oximetry (SPO2) and bispectral index (BIS, Aspect Medical Systems) were applied, meanwhile sodium acetate ringer's injection was infused via internal jugular vein catheter in all participants. Anesthesiologist assistant diluted Dex 200ug (Jiangsu Hengrui Medicine Co., Ltd.) with 0.9% physiological saline 48ml to reach a concentration of 4 ug/mL. Patients in Dex group were administered oxycodone 0.1mg/kg before HIPEC, and then received an intravenous infusion of Dex 1.0 ug/kg/h for 10 min following by a reduced infusion velocity of 0.2 ug/kg/h to maintain until operation completed. Patients in control group were

also administered oxycodone 0.1mg/kg before HIPEC, while infused with the same volume of 0.9% physiological saline at the same rate as the Dex group.

HIPEC was performed using BR-TRG-II type hyperthermic intraperitoneal perfusion therapy system (Guangzhou Baorui Medical Technology Co., Ltd.) 0.9% saline solution 2000-4000ml was infuse into the customized infusion bag and transferred through the infusion tubes over 60 min with a flow velocity of 350–450 mL/min. To obtain the intra-abdominal temperature of 41.5-42.5˚C, inflow temperature was set to 43˚C. The chemotherapeutic agents mixed with the perfusion fluid for HIPEC was cisplatin 80 mg/m2. After HIPEC, the liquids were removed.

2.3 Data Collection

Patient demographics and clinical parameters were collected, including age, gender, body mass index (BMI), hemoglobin (HB), albumin (ALB) and total protein (TP).

Hemodynamic parameters such as heart rate (HR), mean arterial blood pressure (MAP), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were serially recorded at pre-anesthesia (T1), HIPEC begun (T2), 15 min after HIPEC begun (T3), 30 min after HIPEC begun (T4), 45 min after HIPEC begun (T5), end of HIPEC (T6). The mean values of BIS and visual analogue scale (VAS) from T2 to T6 were recorded.

Perioperative characteristics including surgery time, baseline and highest body temperature, fluid volume, urine output and total volume of HIPEC during surgery were also recorded.

Blood samples were collected at baseline (before HIPEC), end of HIPEC and 48 hours after HIPEC. The serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine (Cr), blood urea nitrogen (BUN), uric acid (UA), cystatin C (Cys-C), which represented the functions of liver and kidney were measured. SOD activity and MDA concentration in blood were assessed using specific reagent kits according to the protocols (Nanjing, Jiancheng Bioengineering Institute, China).

2.3 Statistical Analysis

Sample size was calculated by PASS (version 11.0.11; NCSS Statistical Software, Kaysville, UT). The postoperative MDA in patients who underwent HIPEC in our preliminary experiments was 3.30 ± 0.87 nmol/ml. Expecting an improvement of 20% in MDA with Dex administration, 25 patients were required in Dex group which is 25 patients in control group in order to obtain a power of 90%, considering a type I error of 0.05. Data were analyzed using SPSS 23.0 (IBM Corp., Armonk, NY). After Shapiro–Wilk testing for normality of variable distribution, continuous variables were compared between the groups using the independent t-test or Mann–Whitney U test, as appropriate. Categorical variables were compared between the groups using the chi-square or Fisher's exact test, as appropriate. For between-group comparisons of repeated measures including liver and kidney function biomarkers and hemodynamic data, the Brunner–Langer method or linear mixed model was used after normality testing. Group, time and group-by-time as

fixed effects were considered, and times were clustered within patients. A p value < .05 was considered statistically significant.

3. Results

3.1 Demographics and Clinical Characteristics

60 patients were enrolled in our study and 4 patients were excluded according to our exclusion criteria before randomization. All patients were diagnosed as GI cancer. Figure 1 shows the CONSORT diagram of included and excluded patients. The Dex group consisted of 25 patients, including 12 males and 13 females with median age 48.9 years, they are 12 gastric cancer and 13 colorectal cancer patients. 6 patients in control group were withdrawn for refused to draw blood during the research. So it consisted of 25 patients, including 13 males and 12 females with median age 53.8 years, they are 13 gastric cancer and 12 colorectal cancer patients. The information of all 50 residual patients were statistically analyzed (Figure 1). Patient characteristics between the two groups have no statistical differences (p□0.05) (Table 1).

3.2 Intraoperative characteristics changes

Table 2 shows that there were no significant differences in the total surgery time, baseline body temperature, the highest body temperature, and the volume of crystalloid and infusion fluid between the two groups (p>0.05). Compared to the control group, the urine volume of patients in the Dex group were significantly increased (P<0.01).

Intraoperative hemodynamic changes are shown in Figure 2. During HIPEC, HR and blood pressure were obviously reduced after Dex administration (P<0.05). The HR of Dex group were significantly lower than that of control group during HIPEC (P<0.05). There were no significant differences in blood pressure between the two groups.

In addition, We recorded BIS values during HIPEC and calculated the mean value of BIS at 5 time points (T2 to T6). The mean BIS value of patients in Dex group is lower than that in control group (p□0.05). The statistical method of Vas score is the same as that of BIS. Compared with the control group, the patients' Vas scores are lower in Dex group (p□0.05). (Figure 3)

3.3 Variables of liver function

To assess changes in liver function, we examined the associated parameters, such as AST and ALT, which are sensitive indicators of liver damage. As shown in Figure 4, the levels of serum AST and ALT were significant elevated in both groups during HIPEC, however, the elevation of serum AST and ALT could not be alleviated by Dex administration (p>0.05).

3.4 Variables of renal function

To assess changes in renal function, serum Cr, BUN, UA and CYS-C were detected.. As shown in Figure 5, HIPEC significantly increased the levels of serum Cr, UA, Cys-C and BUN in both groups, and notably, serum UA and CYS-C increased up to 48 hours after HIPEC ($p<0.05$). Dex administration obviously alleviated the elevation of serum Cr, UA, Cys-C and BUN ($P<0.05$).

3.5 Variables of MDA and SOD values

As shown in Figure 6, HIPEC significantly increased MDA concentration and decreased SOD activity in both groups and these effects last up to 48h after operation ($p<0.05$). Dex administration significantly decreased MDA concentration and elevated SOD activity ($p<0.05$).

4. Discussion

A growing number of studies suggest that GI malignancies with peritoneal metastasis or malignant ascites are indications for HIPEC, especially in digestive system[10, 11]. A meta-analysis by Sun et al suggests that HIPEC could help to prevent peritoneal recurrence and improve survival of patients with advanced gastric cancer who have received curative tumor resections[12]. Despite its effectiveness has been widely proven by mounting evidence and been included in national cancer guidelines in some European countries, the safety of HIPEC has been controversial. The basis of hyperthermia enhancing chemotherapeutic drugs is related to improving the permeability of drugs to tumor, increasing their cytotoxicity, and delaying their clearance from the abdominal cavity. However, the enhanced effects of hyperthermia and drug toxicity may cause more complications and affect patients prognosis. GI complications after HIPEC ranges from 4 to 19%, the most common ones are anastomotic leaks and fistulas, abdominal abscess and wound infection. Other complications include pleural effusion, pneumonia, acute kidney injury (AKI), hepatic insufficiency, marrow depression, venous thromboembolism and fever[13, 14]. The incidence of AKI after cytoreductive surgery (CRS)-HIPEC have ranged between 2% and 22%[6]. Several cases reported that acute liver failure or necrosis after HIPEC[7, 13]. However, there was no statistical significance of liver fuction in our study. This may reflect the relative good tolerance by decreased hepatic blood flow induced by HIPEC[15]. In terms of pathophysiological changes, hepatic artery blood flow increased when portal blood flow reduced maintain partial hepatic blood flow which followed by adequate liver clearance and oxygen supply. The effect was reversible within 48 hours and did not show up in clinical outcomes[16].

According to the literatures, HIPEC may damage kidney and liver. In present study, we didn't find the liver function of the patients was significantly influenced by HIPEC, which could be demonstrated from the fact that the indexes of liver injury, such as AST and ALT, were not notably increased during perioperative period. While the patients' renal function seems to be affected by HIPEC, UA is the final decomposition product of purine metabolism, its elevation may be a biomarker of renal disease risk. UA was obviously

increased at the end of HIPEC and the 48 hours postoperation, meanwhile, Cys-C, as a new early indicator of AKI, distinctly increased at 48 hours postoperation. At the same time, BUN and Cr has also changed accordingly. To explore whether Dex has a protective effect on liver and kidney, we observed the distinction between groups with/without Dex. The results showed that Dex did not visibly affect the function of liver, but it could significantly alleviated the elevation of serum UA and Cys-C induced by HIPEC and obviously increases patients' urine output, which may be related to the inhibition of oxidative stress.

In present study, we explore the incidence of hepatic insufficiency and AKI in GI cancer patients with HIPEC, we found that the classic functional indexes of liver and kidney have no significant changes during perioperative period, whereas, as a new early indicator of AKI, Cys-C distinctly increased at 48 hours after operation. Cys-C is cleared only via the kidney, and early renal microdamage can lead to change in its serum level. Its serum concentration increase upon mild renal injury and further elevated following the disease progresses[17]. Meanwhile, UA was also obviously increased at the end of HIPEC and the 48 hours post-operation. The elevation of UA is related to AKI and chronic kidney disease, which could cause endothelial dysfunction, intrarenal crystal deposition and and impairment of nitric oxide production. So, we considered that HIPEC may potentially damage the kidney, but it is sometimes overlooked. According to the report, the cytotoxicity of applied agents, intra-abdominal hypertension caused by continuous perfusion, and decreased visceral perfusion, associated with renal injury[18]. As HIPEC drugs, cisplatin or oxaliplatin have a higher risk of AKI[19]. In our center, most patients with GI cancer were treated with cisplatin as chemotherapy during HIPEC, including present study, which may be one reason for increased serum Cys-C level. Nevertheless, other factors such as renal hypoperfusion and ischemia caused by intra-abdominal hypertension and heat stress response may play critical roles in the development of AKI[9, 20]. We inferred that the elevated serum Cys-C, Cr, BUN and UA may related to HIPEC-induced oxidative stress, so the alterations of serum MDA and SOD levels were detected, which are good indicators of the oxidative stress. MDA is one of the most important products of lipid peroxidation and a useful biomarker for oxidative stress[21]. SOD is an antioxidant metal enzyme, which plays a crucial role in the balance between oxidation and antioxidant in the body, its activity reflects the antioxidant capacity of organs. We found that MDA was significantly increased immediately after surgery and 48h post-operation, meanwhile SOD was obviously decreased. These may indicate that oxidative stress was involved in HIPEC-induced renal injury.

Dex is a commonly used sedative in clinical anesthesia. Recently, with in-depth study, its organ-protective properties have gradually emerged[22–23]. Numerous date indicate that Dex provides strong protection against tissue damage caused by hypoxia, oxidative stress and inflammation[24]. It can help several organs, such as brain[25], liver[26], lung[27], heart[28] and kidney[29] against oxidative damage. To confirm whether Dex used during HIPEC could provide liver and kidney protection through antioxidant activity, we compared the serum indicators of the two groups of patients with/without Dex at different time points. We observed that Dex could distinctly alleviate the increase of serum Cys-c, UA and MDA, while effectively elevated the level of serum SOD. Therefore, we believe that Dex protects against subsequent

renal injury by suppressing intraoperative and postoperative oxidative stress. Furthermore, Dex visibly lowered the BIS values and VAS scores of patients during operation, meanwhile notably slowed their heartbeat. These manifestations above are thought to be related to the anti-sympathetic effect of Dex, which inhibits norepinephrine release and reduces plasma catecholamines[30]. For the same reasons, Dex maintains renal perfusion and preserve tubular function by inhibiting the excitability of renal sympathetic nerve, and reduces renin secretion and improves glomerular filtration by activating adrenergic receptors of renal vasculature and tubules [10].

Certain limitations in our study need be addressed. This is a small sample study which limits the possibility of us to detect significant differences between groups. Hyperthermia is a crucial component of HIPEC, however, some researchers believe that sublethal hyperthermia may even cause tolerance to subsequent treatment, and that enhanced oxidative stress can significantly improve the chemotherapeutics to eliminate tumors[31]. Dex alleviates oxidative stress whether have an impact on patients' long-term prognosis requires follow-up. Finally, we did not analyze patients' postoperative complications.

5. Conclusions

Intravenous infusion of Dex significantly alleviated the elevation of serum UA and Cys-C induced by HIPEC and obviously increases patients' urine output, which suggested that it has a protective effect on early renal tubular injury, which may be related to the inhibition of oxidative stress.

Declarations

Ethical approval and consent to participants

All experimental protocols were approved by a ethics committee of guangzhou medical university and ethics licensing committee .This study was conducted at affiliated cancer hospital & institute of guangzhou medical University(23/12/2019), between July 2019 and November 2019 after registration at http://www.chictr.org.cn/ (ChiCTR1900026764)(21/10/2019) and written informed consent was obtained from all subjects and their legal guardians. All the methods were carried out in accordance with the Declaration of Helsinki.

Consent to publication

Not applicable.

Data availability

The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (http://www.chictr.org.cn/), with the approval number as ChiCTR1900026764.The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Funding

The study was funded by the Medical Research Foundation of Guangdong Province (Grant number: B2019035).

Author contribution

Xu Deng: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. RuiMin Luo:Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. Yu Gu: Resources, Conceptualization, Methodology, Validation, Writing–review&editing. YongHua Yao: Conceptualization, Methodology, Validation, Writing – review & editing, Supervision.

Conflict of interest

none.

Acknowledgement

The authors wish to thank qiang ran for his valuable help with our HIPEC questions on this study.

References

1. Duan X, Hong J, Wang F, et al. The influence of ACYP2 polymorphisms on gastrointestinal cancer susceptibility in the Chinese Han population. Mol Genet Genomic Med. 2019;7(7):e00700.
2. Gao LZ, Gao EM, Bai YF, et al. Hyperthermic intraperitoneal chemotherapy plus high-frequency diathermic therapy followed by intravenous chemotherapy versus intravenous chemotherapy alone for postoperative adjuvant treatment of gastrointestinal cancer: a comparative research study. J BUON. 2016;21(6):1510–1517.

3. Fujimura T, Yonemura Y, Fushida S, et al. Continuous hyperthermic peritoneal perfusion for the treatment of peritoneal dissemination in gastric cancers and subsequent second-look operation. Cancer. 1990;65(1):65–71.
4. Yonemura Y, Kawamura T, Bandou E, Takahashi S, Sawa T, Matsuki N. Treatment of peritoneal dissemination from gastric cancer by peritonectomy and chemohyperthermic peritoneal perfusion. Br J Surg. 2005;92(3):370–375.
5. Lehmann K, Rickenbacher A, Jang JH, et al. New insight into hyperthermic intraperitoneal chemotherapy: induction of oxidative stress dramatically enhanced tumor killing in in vitro and in vivo models. Ann Surg. 2012;256(5):730–738.
6. Cata JP, Zavala AM, Van Meter A, et al. Identification of risk factors associated with postoperative acute kidney injury after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: a retrospective study. Int J Hyperthermia. 2018;34(5):538–544.
7. Bouchereau M, Gervais MK, Sideris L, Loriot MH, Ahern SP, Dubé P. Hepatic necrosis and hemorrhage following hyperthermic intraperitoneal chemotherapy with oxaliplatin: A review of two cases. J Gastrointest Oncol. 2011;2(2):113–116.
8. Keating GM. Dexmedetomidine: A Review of Its Use for Sedation in the Intensive Care Setting. Drugs. 2015;75(10):1119–1130.
9. Song Y, Kim DH, Kwon TD, et al. Effect of intraoperative dexmedetomidine on renal function after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a randomized, placebo-controlled trial. Int J Hyperthermia. 2019;36(1):1–8.
10. Lee L, Alie-Cusson F, Dubé P, Sideris L. Postoperative complications affect long-term outcomes after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis. J Surg Oncol. 2017;116(2):236–243.
11. Bhatt A, Sheshadri D, Chandan G, et al. Outcomes of cytoreductive surgery and HIPEC for pseudomyxoma peritonei of appendiceal origin from two Indian centers: A preliminary five-year experience. J BUON. 2017;22(1):251–257.
12. Sun J, Song Y, Wang Z, et al. Benefits of hyperthermic intraperitoneal chemotherapy for patients with serosal invasion in gastric cancer: a meta-analysis of the randomized controlled trials. BMC Cancer. 2012;12:526. Published 2012 Nov 16.
13. Kohli P, Penumadu P, Subramaniam R. Acute Liver Failure Following Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: A Case Report. Cureus. 2019;11(6):e5026. Published 2019 Jun 28.
14. Kang LY, Mok KT, Liu SI, et al. Intraoperative hyperthermic intraperitoneal chemotherapy as adjuvant chemotherapy for advanced gastric cancer patients with serosal invasion. J Chin Med Assoc. 2013;76(8):425–431.
15. Dupont S, Schiffer ERC, White MJ, Diaper JRA, Licker MJ, Masouyé PC. Changes in Hepatic Blood Flow and Liver Function during Closed Abdominal Hyperthermic Intraperitoneal Chemotherapy following Cytoreduction Surgery. Gastroenterol Res Pract. 2018 Mar 12; 2018:8063097.

16. Eipel C., Abshagen K., Vollmar B. Regulation of hepatic blood flow: the hepatic arterial buffer response revisited. World Journal of Gastroenterology. 2010;16(48):6046–6057.
17. Lei L, Li LP, Zeng Z, et al. Value of urinary KIM-1 and NGAL combined with serum Cys C for predicting acute kidney injury secondary to decompensated cirrhosis. Sci Rep. 2018;8(1):7962. Published 2018 May 21.
18. Loggie BW, Thomas P. Gastrointestinal Cancers With Peritoneal Carcinomatosis: Surgery and Hyperthermic Intraperitoneal Chemotherapy. Oncology (Williston Park). 2015;29(7):515–521.
19. Yao X, Panichpisal K, Kurtzman N, Nugent K. Cisplatin nephrotoxicity: a review. Am J Med Sci. 2007;334(2):115–124.
20. Wang CC, Chen F, Kim E, Harrison LE. Thermal sensitization through ROS modulation: a strategy to improve the efficacy of hyperthermic intraperitoneal chemotherapy. Surgery. 2007;142(3):384–392.
21. Verma MK, Jaiswal A, Sharma P, Kumar P, Singh AN. Oxidative stress and biomarker of TNF-α, MDA and FRAP in hypertension. J Med Life. 2019;12(3):253–259.
22. James ML, Olson DM, Graffagnino C. A pilot study of cerebral and haemodynamic physiological changes during sedation with dexmedetomidine or propofol in patients with acute brain injury. Anaesth Intensive Care. 2012;40(6):949–957.
23. Hwang L, Choi IY, Kim SE, et al. Dexmedetomidine ameliorates intracerebral hemorrhage-induced memory impairment by inhibiting apoptosis and enhancing brain-derived neurotrophic factor expression in the rat hippocampus. Int J Mol Med. 2013;31(5):1047–1056.
24. Zhou L, Zhou J, Sheng B, Li X, Yuan Y. Dexmedetomidine exerts dual effects on human annulus fibrosus chondrocytes depending on the oxidative stress status. Biosci Rep. 2019;39(8):BSR20190419. Published 2019 Aug 23.
25. Li F, Wang X, Deng Z, Zhang X, Gao P, Liu H. Dexmedetomidine reduces oxidative stress and provides neuroprotection in a model of traumatic brain injury via the PGC-1α signaling pathway. Neuropeptides. 2018;72:58–64.
26. Tüfek A, Tokgöz O, Aliosmanoglu I, et al. The protective effects of dexmedetomidine on the liver and remote organs against hepatic ischemia reperfusion injury in rats. Int J Surg. 2013;11(1):96–100.
27. Cui J, Zhao H, Wang C, Sun JJ, Lu K, Ma D. Dexmedetomidine attenuates oxidative stress induced lung alveolar epithelial cell apoptosis in vitro. Oxid Med Cell Longev. 2015;2015:358396.
28. Liu XR, Li T, Cao L, et al. Dexmedetomidine attenuates H2O2-induced neonatal rat cardiomyocytes apoptosis through mitochondria- and ER-medicated oxidative stress pathways. Mol Med Rep. 2018;17(5):7258–7264.
29. Kocoglu H, Ozturk H, Ozturk H, Yilmaz F, Gulcu N. Effect of dexmedetomidine on ischemia-reperfusion injury in rat kidney: a histopathologic study. Ren Fail. 2009;31(1):70–74.
30. Tang Q, Wu X, Weng W, et al. The preventive effect of dexmedetomidine on paroxysmal sympathetic hyperactivity in severe traumatic brain injury patients who have undergone surgery: a retrospective study. PeerJ. 2017;5:e2986. Published 2017 Feb 15.

31. Lehmann K, Rickenbacher A, Jang JH, et al. New insight into hyperthermic intraperitoneal chemotherapy: induction of oxidative stress dramatically enhanced tumor killing in in vitro and in vivo models. Ann Surg. 2012;256(5):730–738.

Tables

Tables are available in the Supplementary Files section.

Figures

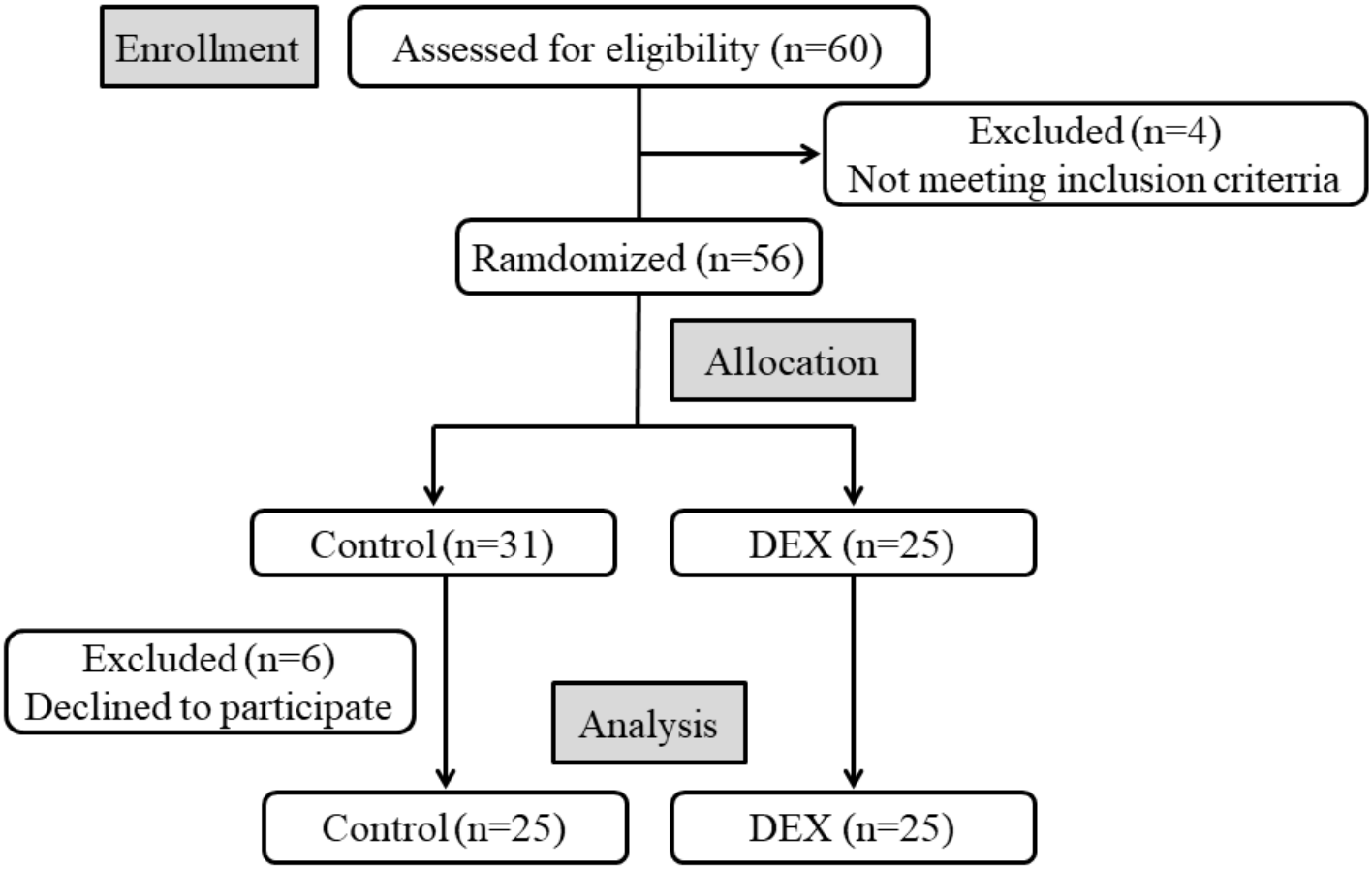

Figure 1. Flow chart of patient selection

Figure 1

Please See image above for figure legend.

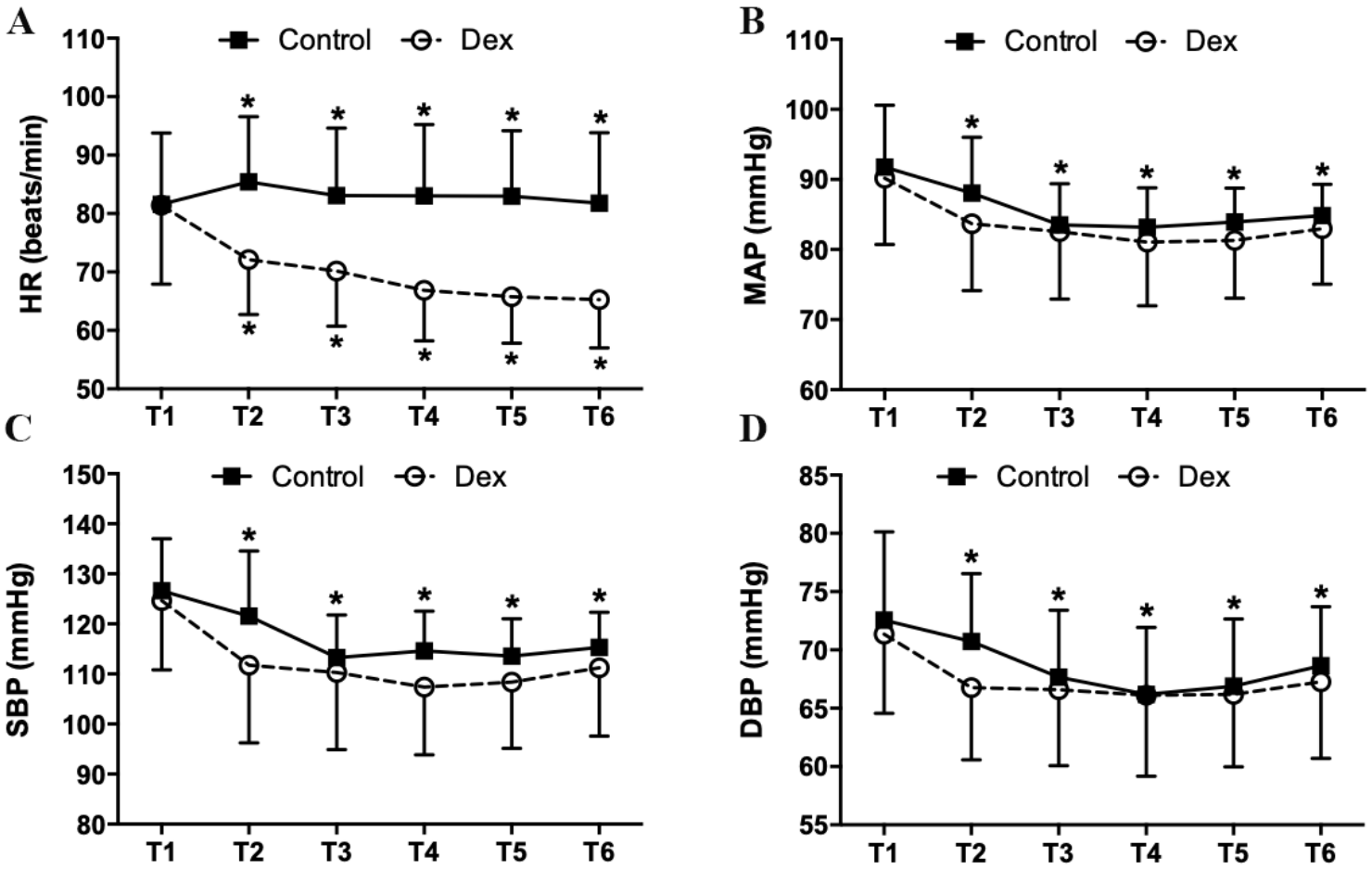

Figure 2. Intraoperative hemodynamic changes. (A) HR (heart rate), (B) MAP (mean arterial blood pressure), (C) SBP (systolic blood pressure), (D) DBP (diastolic blood pressure). T1: pre-anesthesia; T2: HIPEC begun; T3: 15 min after HIPEC begun; T4: 30 min after HIPEC begun; T5: 45 min after HIPEC begun; T6: end of HIPEC. Data are presented as mean ± SD .$^{*}p < 0.05$ versus T1.

Figure 2

Please See image above for figure legend.

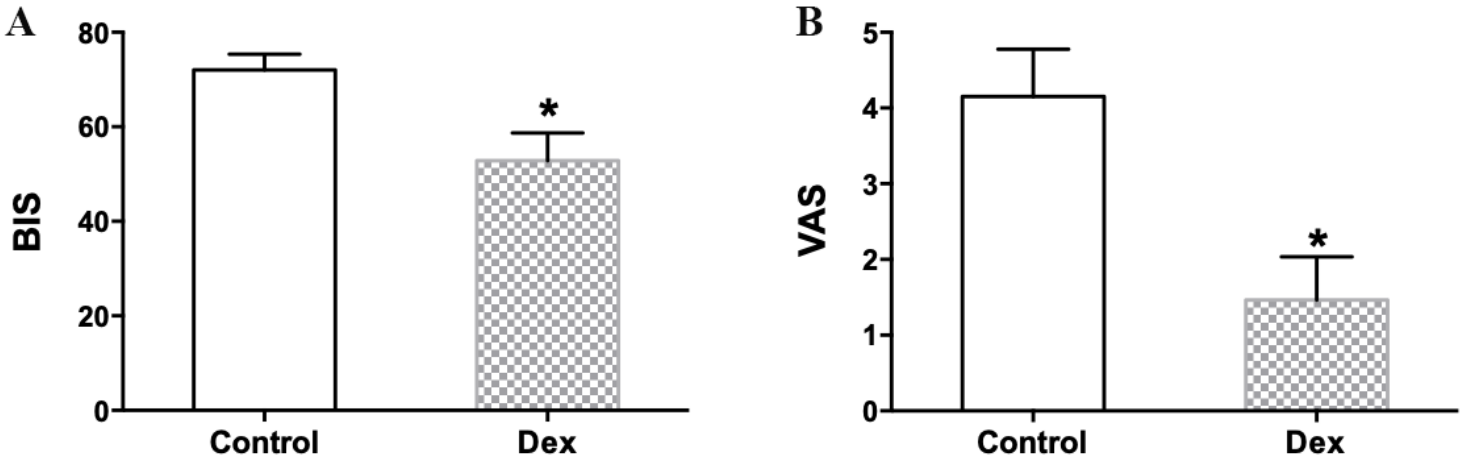

Figure 3. Intraoperative BIS and VAS. (A) BIS (bispectral index), (B) VAS (visual analogue scale). Data are presented as mean ± SD .*$p < 0.05$ versus control group.

Figure 3

Please See image above for figure legend.

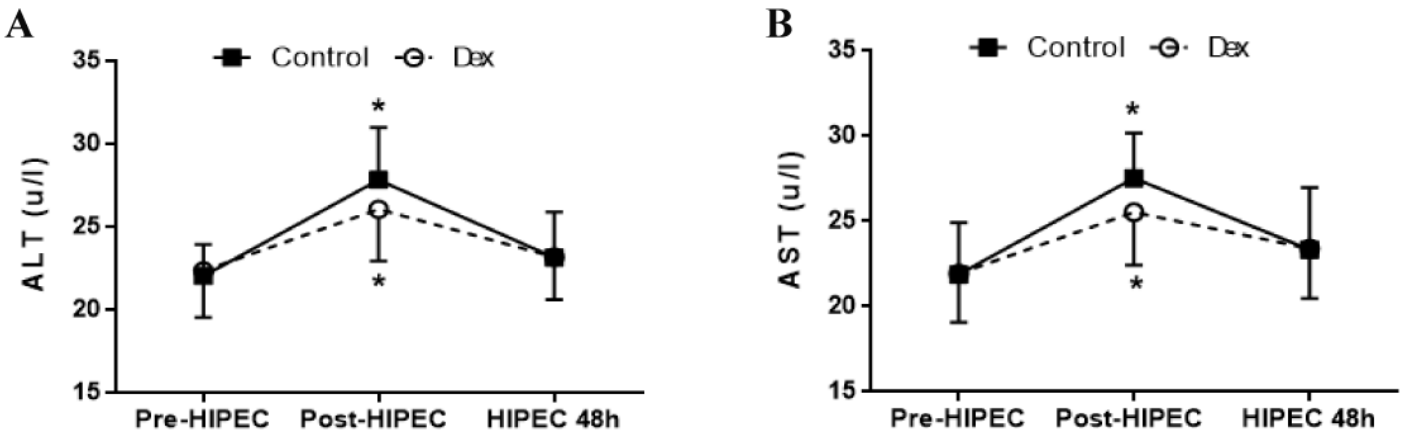

Figure 4. The changes of liver function. (A) ALT (alanine aminotransferase), (B) AST (aspartate aminotransferase). HIPEC : hyperthermic intraperitoneal chemotherapy. Pre-HIPEC: before HIPEC; Post-HIPEC: immediately after HIPEC; HIPEC 48h: 48 hour after HIPEC. Data are presented as mean ± SD .*$p < 0.05$ versus Pre-HIPEC; $^{\$}p < 0.05$ versus Dex group.

Figure 4

Please See image above for figure legend.

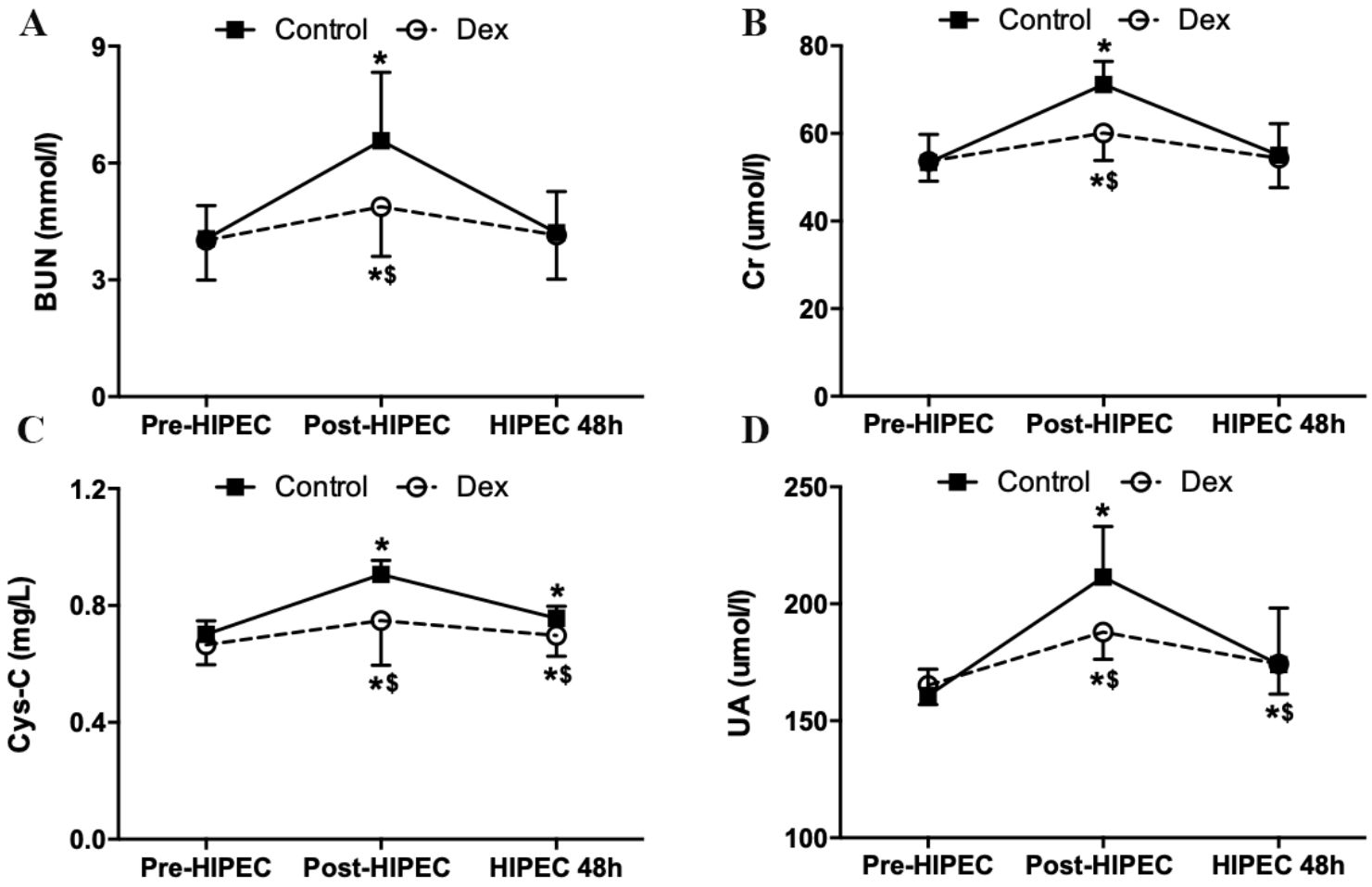

Figure 5. The changes of liver function. (A) BUN (blood urea nitrogen) , (B) Cr (serum creatinine), (C) Cys-C (cystatin C), (D) UA (uric acid). HIPEC : hyperthermic intraperitoneal chemotherapy. Pre-HIPEC: before HIPEC; Post-HIPEC: immediately after HIPEC; HIPEC 48h: 48 hour after HIPEC. Data are presented as mean ± SD.*$p < 0.05$ versus Pre-HIPEC; $^{\$}p < 0.05$ versus Dex group.

Figure 5

Please See image above for figure legend.

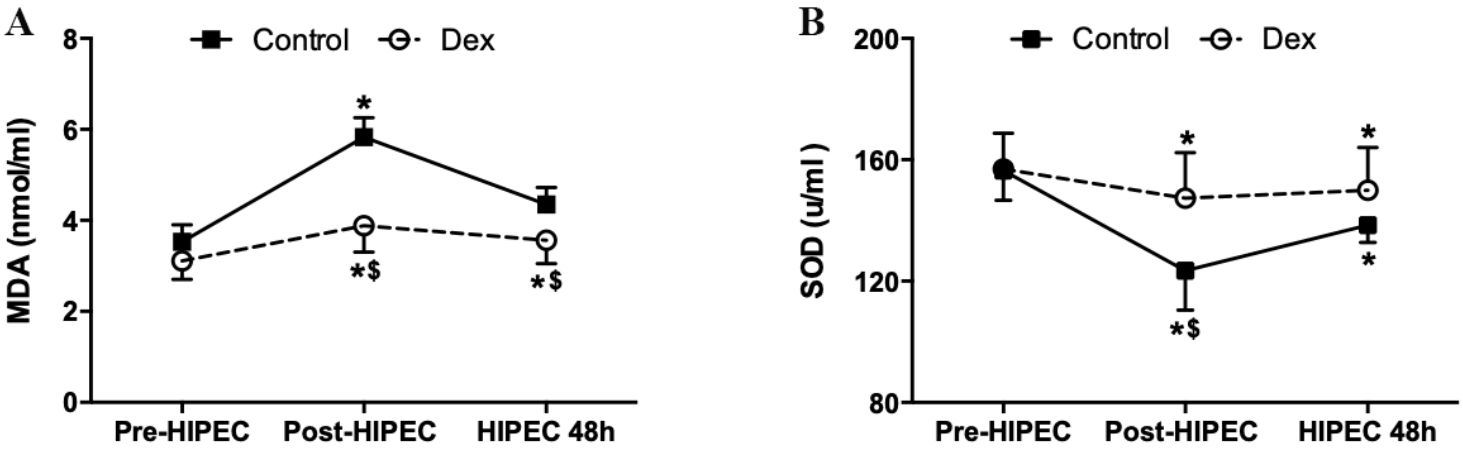

Figure 6. The changes of liver function. (A) MDA (malondialdehyde), (B) SOD (superoxide dismutase). HIPEC : hyperthermic intraperitoneal chemotherapy. Pre-HIPEC: before HIPEC; Post-HIPEC: immediately after HIPEC; HIPEC 48h: 48 hour after HIPEC. Data are presented as mean ± SD .*$p < 0.05$ versus Pre-HIPEC; $^{\$}p < 0.05$ versus Dex group.

Figure 6

Please See image above for figure legend.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 2.tif
- 1.tif