

Effects of dezocine combined with dexmedetomidine on adverse reactions and inflammatory factors in patients undergoing HIPEC after intestinal surgery and its protective effect on the heart in the perioperative period

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Abstract. – OBJECTIVE: The aim of this study was to explore the effects of dezocine combined with dexmedetomidine on adverse reactions and inflammatory factors in patients undergoing hyperthermic intraperitoneal chemotherapy (HIPEC) after intestinal surgery and its protective effect on the heart in the perioperative period.

PATIENTS AND METHODS: A total of 80 patients treated with HIPEC after intestinal surgery in our hospital from September 2018 to December 2019 were enrolled as research subjects. All patients were evenly divided into two groups using a random number table. As to analgesia and sedation during treatment, dezocine was injected intramuscularly at 30 min before treatment in the control group. Meanwhile, dezocine combined with dexmedetomidine was given in the same way in the observation group. Adverse reactions and changes in numeric rating scale (NRS) pain score during intervention were compared between the two groups. The changes in the levels of inflammatory and myocardial injury-related factors, and vascular endothelial function and regeneration ability among cardiovascular indicators at 12 h after intervention were compared as well. Additionally, the correlations of left ventricular mass index (LVMI) with the changes in the levels of inflammatory factor high-sensitivity C-reactive protein (hs-CRP), myocardial injury-related factor lactic dehydrogenase (LDH), vascular endothelial function indicator endothelin-1 (ET-1) and cardiovascular regeneration ability index vascular endothelial growth factor (VEGF) were analyzed.

RESULTS: Compared with control group, the total prevalence rate of severe pain, respiratory depression, nausea and vomiting, diarrhea, and

muscle rigidity during intervention was significantly reduced in the observation group ($p < 0.05$). NRS pain score at 1, 4, 8 and 12 h after intervention decreased remarkably in the observation group compared with the control group ($p < 0.05$). Meanwhile, the levels of inflammatory factors tumor necrosis factor- α (TNF- α) and hs-CRP, and myocardial injury-related factors LDH and creatine kinase MB (CKMB) as well as ET-1 at 12 h after intervention declined remarkably in observation group compared with control group ($p < 0.05$). However, the levels of nitric oxide (NO), VEGF and basic fibroblast growth factor (bFGF) rose significantly in the observation group ($p < 0.05$). Besides, LVMI was positively correlated with hs-CRP and LDH, whereas was negatively associated with ET-1 and VEGF ($p < 0.05$).

CONCLUSIONS: In HIPEC, dezocine combined with dexmedetomidine used for sedation and analgesia is able to effectively reduce adverse reactions and relieve inflammatory responses *in vivo*, exerting a cardio-protective effect.

Key Words:

Dexmedetomidine, Hyperthermic intraperitoneal chemotherapy (HIPEC), Intestinal surgery, Dezocine, Adverse reactions, Inflammatory responses, Cardioprotection.

Introduction

Hyperthermic intraperitoneal chemotherapy (HIPEC) refers to the infusion of chemotherapeutic drugs heated to 43°C into the abdominal cavity through the abdominal catheter¹ to prevent

and treat malignant tumors of abdominal organs. Currently, it is one of the most important adjuvant treatment approaches for abdominal malignant tumors. Meanwhile, HIPEC is of great significance for the prevention and treatment of transcoelomic spread of malignant tumors². During HIPEC, adverse reactions, such as pain, nausea, vomiting, and diarrhea often occur due to multiple stimuli, including high temperature (43°C) and chemotherapy drugs³. Besides, large doses of normal saline perfused during HIPEC leads to abdominal cavity expansion, diaphragm elevation and catheter traction, eventually resulting in aggravated pain in patients. For this reason, strengthening sedative and analgesic interventions is necessary for patients during treatment⁴.

In clinical practice, large-volume ascites is often detected in patients undergoing HIPEC. This may lead to diaphragm elevation and inhibit the respiratory and circulatory functions of patients to some extent⁵. During treatment, keeping spontaneous breathing and maintaining stable circulatory function are extremely important⁶. Previous studies have reported that opioid analgesics have a satisfactory analgesic effect. However, they are easy to result in respiratory depression and can affect circulatory function. In recent years, Dezocine is considered as an opioid receptor agonist/antagonist able to be injected intramuscularly or intravenously. It shows a good analgesic effect, with few adverse reactions. However, its simple application achieves an ineffectively sedative effect⁷. Dexmedetomidine, a highly-selective α_2 -adrenergic receptor agonist, has good analgesic and sedative effects⁸. Dezocine, a synthesized bridged aminotetralin, is used for pain management. Dezocine is becoming dominated in China for relieving moderate to severe pain⁹⁻¹².

In this study, we aimed to explore the effects of dezocine combined with dexmedetomidine on adverse reactions and inflammatory factors in patients undergoing HIPEC after intestinal surgery and its protective effect on the heart in the perioperative period.

Patients and Methods

General Data

A total of 80 patients treated with HIPEC after intestinal surgery in our hospital from September 2018 to December 2019 were enrolled as research subjects. Before enrollment, all patients signed the informed consent. This study was approved by the

Ethics Committee of Sanmen Hospital of Traditional Chinese Medicine. Inclusion criteria were as follows: patients aged 18-65 years old, those without abnormal mental status, those with good nutritional status, those with normal intestinal function in the past, and those with American Society of Anesthesiologists (ASA) class II-III. Exclusion criteria were as follows: patients with mental disorder, those with severe arrhythmia, those with systemic infection, those with severe liver and renal dysfunction, those who were allergic to drugs used in this study, or those with intestinal obstruction, heart failure or myocardial infarction in the past. All enrolled patients were divided into two groups using a random number table, namely observation group (n=40) and control group (n=40). In observation group, there were 23 males and 17 females aged 19-65 years old, with an average of (53.3±3.7) years old. This group included 28 cases of colon cancer and 12 cases of rectal cancer, 24 cases of ASA class II and 16 cases of ASA class III, and 21 cases of hypertension, 18 cases of coronary heart disease, 16 cases of hyperlipidemia, 19 cases of chronic obstructive pulmonary disease, and 20 cases of diabetes. In control group, there were 24 males and 16 females aged 18-65 years old, with an average age of (53.2±3.7) years old. As to primary disease, there were 27 cases of colon cancer and 13 cases of rectal cancer. In terms of ASA classification, there were 25 cases of ASA class II and 15 cases of ASA class III. Based on common medical diseases, there were 20 patients with hypertension, 17 patients with coronary heart disease, 15 patients with hyperlipidemia, 18 patients with chronic obstructive pulmonary disease, and 20 patients with diabetes. There were no statistically significant differences in gender, age, primary disease, ASA classification and common medical diseases between the two groups ($p>0.05$).

HIPEC

All enrolled patients received HIPEC. With an intracavity hyperthermia instrument (BRTRG II, Guangzhou Bright Medical Technology Co., Ltd., Guangzhou, China, temperature: 43°C), the prepared chemotherapeutic drug was diluted with 0.9% normal saline. Subsequently, it was continuously perfused into the abdominal cavity with a pressure pump *via* two inlet tubes under the diaphragm and two outlet tubes in left and right iliac fossa. Each treatment lasted for 90 min.

Analgesia and Sedation During Treatment

In control group, 5 mg of dezocine (Yangtze River Pharmaceutical Group, Taizhou, China, lot

number: 1808113) was intramuscularly injected at 30 min before treatment. Subsequently, 20 mg of dezocine was dissolved in 0.9% normal saline to prepare 50 mL solution that was continuously and intravenously pumped. The rate was adjusted according to the degree of pain using intravenous infusion pumps. In the observation group, dezocine was given in the same way. Combined with dexmedetomidine (4 µg/mL, Jiangsu Chenxin Pharmaceutical, Jining, China, lot number: 1807023), dezocine was continuously and intravenously pumped at 1 µg/kg. After about 10 min, the dosage was adjusted to 0.02-0.04 µg/kg, and the intravenous pumping was continued.

Observation Indexes

Adverse reactions and changes in numeric rating scale (NRS) pain score during intervention were compared between the two groups. The changes in the levels of inflammatory and myocardial injury-related factors, and vascular endothelial function and regeneration ability among cardiovascular indicators at 12 h after intervention were compared as well. Additionally, the correlations of left ventricular mass index (LVMI) with the changes in the levels of inflammatory factor high-sensitivity C-reactive protein (hs-CRP), myocardial injury-related factor lactic dehydrogenase (LDH), vascular endothelial function indicator endothelin-1 (ET-1) and cardiovascular regeneration ability index vascular endothelial growth factor (VEGF) were analyzed.

Evaluation Criteria

Inflammatory factors tumor necrosis factor-α (TNF-α, normal value: 5-100 ng/L) and hs-CRP (normal value: ≤10 mg/L) were detected via double antibody sandwich in one step method and latex-enhanced turbidimetric immunoassay, respectively. As to cardiovascular function, vascular endothelial function and vascular regeneration ability were observed. Vascular endothelial function indexes included ET-1 (normal value: 43.5-58.4 ng/L) and nitric oxide (NO, normal value: 13.8-34.6 µmol/L). Regeneration ability

indicators VEGF (normal value: 55.0-90.0 ng/L) and basic fibroblast growth factor (bFGF, normal value: 36.9-58.8 ng/L) were determined in strict accordance with ELISA. Myocardial injury-related indicators included LDH (normal value: 100-240 U/L), creatine kinase MB (CKMB, normal value: 0-25 IU/L) and troponin I (cTnI, normal value: <0.1 µg/L). LVMI (normal value: 120-125 g/m²) was assessed by a physician with a title of associate senior or above based on relevant indicators obtained through a color Doppler diagnostic apparatus (Mindray ATL5000, Shenzhen, China).

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$). The *t*-test was used for comparison of the mean between two groups. Percentage (%) was used to express the enumeration data and chi-square test was used for data analysis. *p*<0.05 was considered statistically significant.

Results

Comparison of Prevalence of Adverse Reactions During Intervention Between the Two Groups

The total rate of severe pain, respiratory depression, nausea and vomiting, diarrhea, and muscle rigidity was significantly lower in the observation group than that in the control group (*p*<0.05) (Table I).

Changes in NRS Pain Score During Intervention

NRS pain score before intervention was (5.5±0.2) points in observation group and (5.6±0.2) points in control group, respectively. The results showed that NRS pain score was significantly lower in observation group than control group at 1 h, 4 h, 8 h and 12 h after intervention [(2.3±0.2) points vs. (3.8±0.4) points,

Table I. Comparison of incidence of adverse reactions during intervention between the two groups (n).

	Severe pain	Respiratory depression	Nausea and vomiting	Diarrhea	Muscle rigidity	Total incidence rate
Observation group	1	0	1	1	1	4 (10.0%)
Control group	6	3	3	1	3	16 (40.0%)
χ^2	-					8.067
<i>p</i>	-					0.005

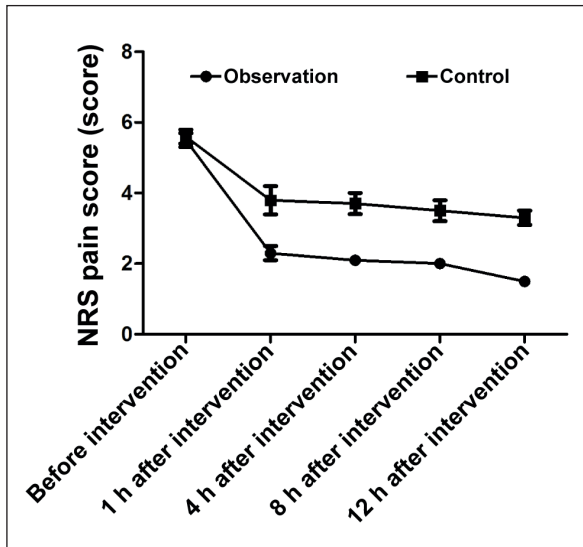


Figure 1. Changes in NRS pain score during intervention.

(2.1±0.1) points vs. (3.7±0.3) points, (2.0±0.1) points vs. (3.5±0.3) points, and (1.5±0.1) points vs. (3.3±0.2) points, $t=21.213, 32.000, 30.000$ and $50.912, p<0.001$] (Figure 1).

Comparison of Inflammatory Factor Level at 12 h after Intervention Between the Two Groups

The levels of inflammatory factors TNF- α and hs-CRP in observation group were notably lower than those in control group at 12 h after intervention ($p<0.05$) (Table II, Figure 2).

Comparison of Myocardial Injury-Related Factor Content at 12 h After Intervention Between the Two Groups

At 12 h after intervention, the levels of myocardial injury-related factors LDH and CKMB were notably lower in the observation group than those in the control group ($p<0.05$). However, no statistically significant difference was observed in the level of cTnI between the two groups ($p>0.05$) (Table III, Figure 3).

Table II. Comparison of inflammatory factor level at 12 h after intervention between the two groups ($\bar{x}\pm s$).

	TNF- α (ng/L)	Hs-CRP (mg/L)
Observation group	53.1±2.3	50.2±3.7
Control group	118.2±37.4	166.4±13.7
<i>t</i>	93.774	51.788
<i>p</i>	<0.001	<0.001

Comparisons of Vascular Endothelial Function and Regeneration Ability Among Cardiovascular Indexes at 12 h After Intervention Between the Two Groups

In comparison with control group, observation group exhibited significantly elevated levels of NO, VEGF and bFGF ($p<0.05$) and reduced level of ET-1 ($p<0.05$) at 12 h after intervention (Table IV, Figure 4).

Correlations of LVMI with Changes in Levels of hs-CRP, LDH, ET-1 and VEGF

LVMI was positively correlated with hs-CRP and LDH levels ($p<0.05$) and was negatively associated with ET-1 and VEGF levels ($p<0.05$) (Table V, Figure 5).

Discussion

HIPEC is an adjuvant therapy for malignancy tumors of the abdominal cavity, in which chemotherapeutic drugs are continuously and intraperitoneally infused together with warm saline¹³. Through peritoneal lavage with chemotherapy drugs and high temperature treatment, it can effectively kill cancer cells and prevent postoperative recurrence, especially transcoelomic spread¹⁴. Previous studies have shown that HIPEC increases body temperature, heart rate and blood pressure, and changes vital signs of patients¹⁵. To reduce HIPEC-induced stress on the body of patients, effective sedation and analgesia are fundamental. Meanwhile, it is essential to retain spontaneous breathing and maintain stable circulatory function of patients during sedation and analgesia¹⁶. As a highly-selective α_2 -adrenergic receptor ag-

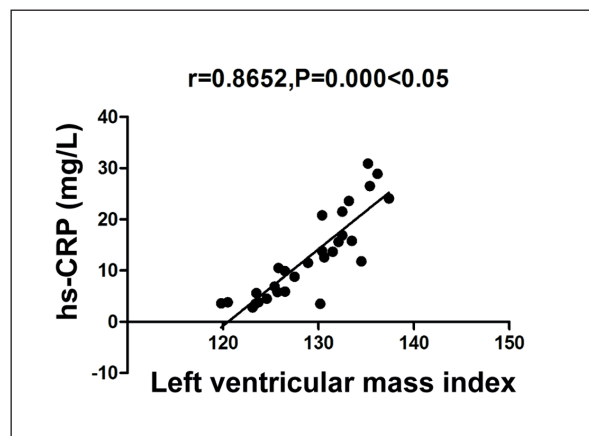


Figure 2. Relationship between LVMI and hs-CRP level.

Table III. Comparison of myocardial injury-related factor content at 12 h after intervention between the two groups ($\bar{x}\pm s$).

	LDH (U/L)	CKMB (IU/L)	cTnl (ng/mL)
Observation group	237.4±37.4	21.2±1.5	0.03±0.01
Control group	384.4±43.7	56.6±5.1	0.03±0.02
<i>t</i>	16.163	42.116	0.000
<i>p</i>	<0.001	<0.001	1.000

onist widely applied in clinical practice, dexmedetomidine is able to induce physiological sleep. In addition, it exerts an evident analgesic effect *via* intravenous pumping¹⁷, with a short half-life. Numerous studies have also indicated that dexmedetomidine has anti-anxiety and anti-sympathetic effects and can inhibit stress responses¹⁸. A previous report¹⁹ showed that dexmedetomidine may have protective effects against early tubular injury in HIPEC. Another Double-Blind Randomized Controlled Trial indicated that the continuous intraoperative infusion of dexmedetomidine in patients undergoing cytoreductive surgery with HIPEC did not significantly lower the inflammatory indices²⁰.

To effectually improve the sedative and analgesic effects of patients undergoing HIPEC, intravenous pumping of the combination with dexmedetomidine was adopted in observation group in addition to the use of dezocine in control group. The prevalence of adverse reactions during intervention was compared between the two groups. It was found that the total occurrence rate of severe pain, respiratory depression, nausea and vomiting, diarrhea, and muscle rigidity was significantly lower in observation group than that in control group. This demonstrates that in HIPEC, dezocine combined with

dexmedetomidine is able to effectively reduce adverse reactions during sedation and analgesia. Besides, the comparison of NRS pain score changes during intervention revealed that NRS pain score was notably lower in observation group than control group at 1, 4, 8 and 12 h after intervention. These findings imply that in HIPEC, dezocine combined with dexmedetomidine used for sedation and analgesia can significantly alleviate pain and improve therapeutic comfort. Subsequently, the levels of inflammatory factors were compared at 12 h after intervention between the two groups. The results uncovered that the levels of TNF- α and hs-CRP in the observation group were significantly lower than those in control group. This suggests that in HIPEC, dezocine combined with dexmedetomidine possesses a positive significance for reducing inflammatory responses in the body. Moreover, the content of myocardial injury-related factors was compared at 12 h after intervention between the two groups. It was discovered that the content of LDH and CKMB was remarkably lower in the observation group than that in the control group. These results demonstrated that in HIPEC, dezocine combined with dexmedetomidine can improve myocardial function of patients to some extent. Furthermore, vascular endothelial function and regeneration ability among cardiovascular indexes at 12 h after intervention were compared between the two groups. The results demonstrated that in comparison with control group, observation group exhibited remarkably elevated levels of NO, VEGF and bFGF and reduced level of ET-1. This indicates that in HIPEC, dezocine combined with dexmedetomidine has an important value in ameliorating cardiovascular endothelial function and enhancing cardiovascular regeneration ability. The correlations of LVMI with inflammatory factors, myocardial injury-related factors, and vascular endothelial function and cardiovascular regeneration ability indexes were finally analyzed. The results showed that LVMI was positively correlated

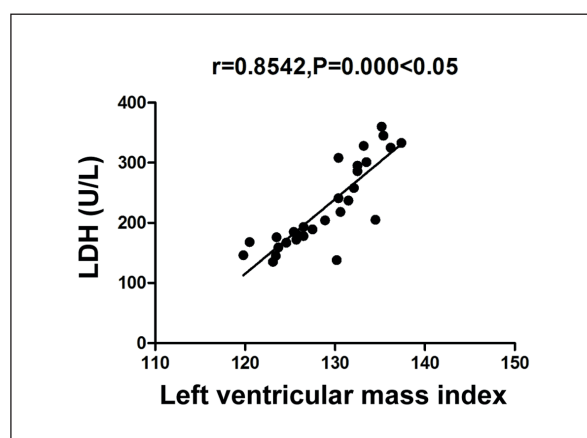


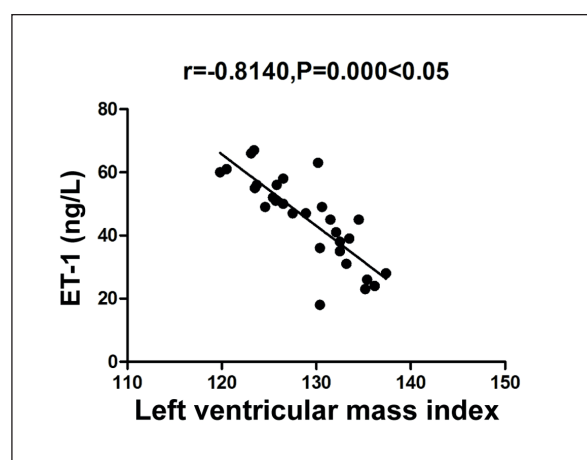
Figure 3. Relationship between LVMI and LDH level.

Table IV. Comparisons of vascular endothelial function and regeneration ability among cardiovascular indexes at 12 h after intervention between the two groups ($\bar{x}\pm s$).

	ET-1 (ng/L)	NO ($\mu\text{mol/L}$)	VEGF (ng/L)	bFGF (ng/L)
Observation group	27.6 \pm 2.5	59.9 \pm 10.5	85.6 \pm 6.8	43.7 \pm 3.7
Control group	60.1 \pm 5.3	37.4 \pm 1.4	49.7 \pm 3.7	25.6 \pm 1.7
<i>t</i>	35.076	13.434	29.329	28.114
<i>p</i>	<0.001	<0.001	<0.001	<0.001

with hs-CRP and LDH levels and negatively associated with ET-1 and VEGF levels.

In HIPEC, dezocine combined with dexmedetomidine can effectively reduce the prevalence rate of adverse reactions, relieve inflammatory responses *in vivo*, and improve heart function compared with dezocine alone²¹. Meanwhile, dexmedetomidine can induce physiological sleep, decrease the effect on respiratory function, slow down the heart rate to some extent, inhibit catecholamine secretion and reduce the impact on hemodynamics, thus protecting the cardiovascular system²². Currently, it is widely applied for sedation during the perioperative period in the anesthesiology department and intensive care unit. Meanwhile, it is able to distinctly lower the dosage of opioid receptor agonists²³, exerting a remarkable complementary analgesic effect. In addition, the continuously intravenous pumping of dexmedetomidine can reduce nausea and vomiting, attenuate respiratory depression to a certain extent²⁴, and decrease the side effects like muscle rigidity caused by opioids. The application of dexmedetomidine in patients receiving HIPEC²⁵, combined with the condition of individuals, reduces psychological and physiological stress and improves overall treatment comfort²⁶.

**Figure 4.** Association between LVMI and ET-1 level.

Conclusions

The novelty of this study was that dezocine combined with dexmedetomidine used for sedation and analgesia is able to effectively reduce adverse reactions and relieve inflammatory responses *in vivo*, exerting a cardio-protective effect in HIPEC.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Table V. Correlations of LVMI with changes in levels of hs-CRP, LDH, ET-1 and VEGF.

	<i>r</i>	<i>P</i>
Hs-CRP	0.8652	<0.001
LDH	0.8542	<0.001
ET-1	-0.8140	<0.001
VEGF	-0.8382	<0.001

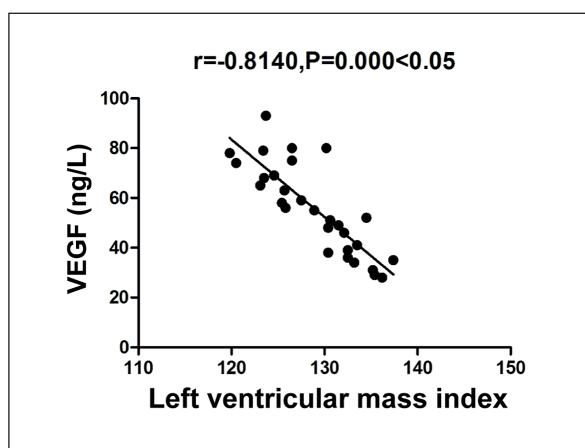


Figure 5. Correlation between LVMI and VEGF level.

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