DEXMEDETOMIDINE PROMOTES RAPID RECOVERY OF PATIENTS UNDERGOING RADIAL COLON CANCER RESECTION THROUGH REGULATING CYTOKINE EXPRESSION: A RANDOMIZED, CONTROLLED, PROSPECTIVE STUDY

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ABSTRACT

Introduction*: The role of dexmedetomidine in recovery of patients undergoing radical colon cancer resection is unknown, and this study served to investigate its role and mechanism.*

Materials and methods*: This randomized, controlled, blinded, prospective study enrolled 80 patients undergoing laparoscopic radical resection of colon cancer into two groups: dexmedetomidine (n=40) and control (n=40). Dexmedetomidine was given 0.5 ug.kg-1 for ten minutes and maintained at 0.4 ug.kg-1 per hour. Serum TGF-β, ICAM-1, TNF-α, IL-6, and C-reactive protein were analyzed after anesthesia as the primary outcome and the role in promoting patient recovery as the secondary outcome.*

Results*: Compared with the control group, the dexmedetomidine group had greater TGF-β (1757.05±139.75 vs. 1566.14±141.32 pg/ml, P<0.05) but lower ICAM-1 (322.47±39.12 vs. 405.15±49.71 ng/ml, P<0.05), IL-6 (123.50±10.34 vs. 150.30±12.69 pg/mL), and TNF-α (43.87±4.61 vs. 58.93±5.46 pg/mL). The dexmedetomidine group had decreased C-reactive protein on the first day after operation (36.65±8.05 vs. 54.70±7.21mg/l, P<0.05), reduced 24-h drainage volume (97.25±23.67 vs. 198.25±36.03 ml, P<0.05), shortened time to get out of bed (23.60±3.21 vs. 34.17±3.84h, P<0.05), quicker recovery of bowel sounds (61.30±6.04 vs. 85.35±8.38 h, P<0.05), quicker anal exhaust (65.15±6.10 vs. 89.48±8.32 h, P<0.05) and shortened hospital stay (6.58±0.65 vs. 7.85±0.86 d, P<0.05). The ROC curve analysis revealed a high area under the curve > 0.9 for all these parameters.*

Conclusion*: Dexmedetomidine can promote the healing of surgical wound and reduce the occurrence of postoperative adhesion by regulating the expression of cytokines, which is conducive to the rapid recovery of patients with colon cancer.*

Keywords: *Dexmedetomidine, Colon cancer, Cytokine, Laparoscopy.*

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Introduction

As a novel and highly selective agonist of α2 adrenergic receptor with a short elimination half-life, dexmedetomidine is non-addictive and can produce dose-dependent sedative, anxiolytic, and analgesic effects besides the anti-sympathetic and anti-shivering properties[1]. It can also be applied for semi-arousable and cooperative sedation to promote sedative and analgesic effects, maintain hemodynamic stability and decrease necessary dose of other analgesic agents. Dexmedetomidine has been used as fast-track management in cardiac surgery, endovascular embolization procedures for intracranial aneurysms and spinal surgery in humans and surgical procedures in animal experiments[1,2]. Fast-track anesthetic management leads to fast recovery from general anesthesia, which is critical for management of adverse events. For patients who underwent abdominal surgery, intraperitoneal

adhesions are a frequent event and a leading cause of serious conditions including bowel obstruction, pelvic pain and infertility, severely affecting the quality of life of millions of people across the world[3]. Intraperitoneal adhesions are caused by fibrous tissue bands within the peritoneal cavity because of inflammation or surgical manipulation, and this process is critically affected by a limited number of cells and molecules in the mechanisms of occurrence[4]. Prevention of postoperative peritoneal adhesions is associated with decreased release of tumor necrosis factor (TNF-α) and interleukin (IL) -1α in a rat animal experiment[5]. After studying the effect of dexmedetomidine anesthesia on perioperative levels of TNF-α and IL-6 in ovarian cancer patients treated with radical resection, Liu et al found that the serum TNF-α and IL-6 levels were significantly decreased in the dexmedetomidine group[4]. The study by Fang et al6 found that decreased production of fibrin-induced inflammatory cytokines like IL-6 could prevent post-surgical peritoneal adhesions.

Moreover, fibrin laid upon peritoneal mesothelial cells in culture to mimic intraperitoneal adhesion demonstrated increased expression of IL-6, IL-1β, TNF-α and vascular endothelial growth factor (VEGF)-A rather than increased expression of tumor growth factor (TGF)β1 and VEGF-C6. TGF-β1 and IL-6 have been found increased in the peritoneal fluid of patients who had undergone abdominal surgery[3]. The expression of intracellular adhesion molecule-1 (ICAM-1) is also increased in a rat model of cerebral ischemia-reperfusion, and the use of dexmedetomidine can significantly alleviated ischemia-reperfusion damage to the rat brains via decreasing nuclear factor-kappa B (NF-kB) and ICAM-17. Currently, there are few reports which are related to the cytokines in the inflammatory process in patients treated with abdominal surgery, and the effect of dexmedetomidine on prevention of intraperitoneal adhesions via adjusting the cytokines and on fast recovery of the patients is unknown.

It has been hypothesized that dexmedetomidine promotes fast recovery of patients undergoing laparoscopic radical resection of colon cancer and prevents intraperitoneal adhesion by regulating the levels of serum cytokines. Therefore, this study was performed in order to investigate the effects of dexmedetomidine on fast recovery after surgery and on serum cytokines of TGF-β, ICAM-1, TNF-α, and IL-6 in patients undergoing laparoscopic resection of colon cancer. The primary outcome was the regulating effect of dexmedetomidine on serum cytokines, and the secondary outcome was its effect on promoting fast recovery of these patients.

Methods

This randomized, controlled, blinded, prospective study was approved by the ethics committee of Shijiazhuang People's Hospital on June 11, 2018 with the record number 20180631, and all the patients had provided written informed consent to participate. Between August 2019 and May 2020, patients who underwent selective laparoscopic radical resection of colon cancer were enrolled. The inclusion criteria were patients with colon cancer and ASA-PS (American Society of Anesthesiologists Physical Status) grades of I-II8 but without history of severe bradycardia, atrioventricular block, liver and kidney dysfunction. The exclusion criteria were patients with severe bradycardia, atrioventricular block and hepatorenal dysfunction. The ASA-PS grading system is an approach to characterize the operative risk of patients before anesthesia in every surgical procedure[8]. All patients underwent colonoscopy before operation, with the histopathological diagnosis being colon cancer. There were eighty patients with an age range of 38-89 years (mean 62.5 ± 5.5) and a weight range of 51-83 (68.3 ± 5.2) kg. The patients were randomly divided into the dexmedetomidine or control group with 40 patients in each group (Table 1).

Groups	No.	Age (y)	Sex(M/F)	Weight (kg)	ASA grading (I/II)	Operation time (min)	Infusion volume (ml)
DEX	40	61.7±5.4	12/8	67.46±4.9	4/16	218.5±27.5	1942.3±43.8
Control	40	63.5±6.3	13/7	68.5±5.3	3/17	213.3±25.4	1905.5±52.4

Table 1: Comparison of general data between two groups. *Note: DEX, dexmedetomidine. No significant (P>0.05) difference existed between the two groups.*

In the randomization process, the random number table method was used for grouping: first, 80 patients were numbered from 1 to 80, then 3 digits were read as a random number from any row or column in the random number table, and then all the selected random numbers were numbered from small to large.

The patient was positioned in the supine position, with routine ECG monitoring, invasive radial artery blood pressure measurement, oxygen saturation monitoring, and mask oxygen inhalation. General anesthesia was applied in all patients. For the control group, midazolam 0.04 mg.kg-1, sufentanil 0.4 ug.kg-1, propofol 1.5 mg.kg-1, and cisatracurium 0.2 mg.kg-1 were administered in

order for anesthesia induction. During the operation, sevoflurane was inhaled, sufentanil was added intermittently for analgesia, and cisatracurium was used to maintain muscle relaxation. The anesthesia depth was maintained at 40-60 in the Bispectral index of EEG during the operation. After the operation, the patient was recovered in the anesthesia recovery roomIn the dexmedetomedine group, before anesthesia induction, dexmedetomidine was given 0.5 ug.kg-1 for ten minutes, maintained at 0.4 ug.kg-1 per hour, and stopped half an hour before the end of operation. Other anesthetics were used in the same doses as in the control group. During the operation, atropine 0.5 mg was injected intravenously when the heart rate was <50 bpm, and intravenous injection of 20-40μg of norepinephrine was administered when the arterial systolic pressure was lower than 90 mm Hg or 30% lower than the basic blood pressure. Sodium acetate Ringer's solution and hydroxyethyl starch were infused during the operation.

The laparoscopic surgery was performed by the same team of surgeons. After successful general anesthesia, the patient took mild lithotomy position with the head down and foot high, and pneumoperitoneum was established with the pneumoperitoneum pressure being adjusted at 11-14 mmHg. Laparoscopic exploration was firstly performed to identify the tumor site. Then, the laparoscopic surgery was conducted with five holes, the tissue around the tumor was dissociated with ultrasonic scalpel, and the severed blood vessels were clipped. The median incision in the length of 8 cm of the upper abdomen was performed, the intestinal tube containing the tumor was removed, and the stapler was used for intestinal anastomosis. The abdominal cavity was carefully washed, and the abdomen cavity was closed after the drainage tube was placed.

The serum transforming growth factor - β (TGF - β), contents of intercellular adhesion molecule (ICAM-1), tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and C-reactive protein were analyzed. Four milliliter venous blood was collected before dexmedetomidine was stopped half an hour prior to the end of laparoscopic surgery, and then it was centrifuged at 3000 rotations per minute for 20 minutes. The supernatant was then taken and frozen at - 80 °C. The serum TGF - β was detected by ELISA, and the normal range of the kit was 800-1800pg.ml-1. The contents of ICAM-1, TNF-α, and IL-6 were measured. C-reactive protein on the first day after operation, 24-hour drainage volume, the first time to get out of bed, recovery time of bowel sounds, first anal exhaust time and postoperative hospital stay were compared between the two groups.

The statistical analysis was performed with the SPSS (Version 23.0, IBM, Chicago, IL, USA). The measurement data were expressed as mean ± standard deviation if in normal distribution and tested with the t test. The enumeration data were expressed as numbers and percentages and were tested with the Chi square test. The receiver operating characteristic (ROC) curve was used to analyze the predictive value of each index. The significant P was set at <0.05. The sample sizes of this study were determined based on the following considerations[5]. After a pilot study in 10 patients, we settled on a mean difference in TGF-β of 150 pg.ml-1 between the two groups (1643.28±153.27 for dexmedetomidine and 1492.85 ± 158.26 for the control group), which indicated that at least 28 patients were needed per group for this study according to the statistical method. This sample size was calculated using two-sided analysis with an alpha risk set at 5% and the power at 95%[9].

Results

No significant difference existed in the age (61.7±5.4 vs. 63.5±6.3 years), ASA grades (4/16 vs. 3/17), operation duration (218.5±27.5 vs. 213.3±25.4 min), and infusion volume (1942.3±43.8 vs. 1905.5±52.4) between the two groups (P>0.05) (Table 1). Compared with the control group, the dexmedetomidine group had significantly greater TGF-β (1757.05±139.75 vs. 1566.14±141.32 pg.ml-1) (P<0.05) but significantly lower ICAM-1 (322.47±39.12 vs. 405.15±49.71 ng.ml-1), IL-6 (123.50±10.34vs. 150.30±12.69 pg.ml-1), and TNF-α (43.87±4.61 vs. 58.93±5.46 pg.ml-1) (P<0.05) (Table 2).

Groups	TGF-β(pg.ml^{-1})	ICAM-1 (ng.ml^{-1})	TNF-α(pg.mL^{-1})	IL-6 (pg.mL^{-1})
DEX	1757.05±139.75*	322.47±39.12*	43.87±4.61*	123.50±10.34*
Control	1566.14±141.32	405.15±49.71	58.93±5.46	150.30±12.69

Table 2: Biomarkers in two groups (mean± standard deviation , n=40 in each group).

*Note: DEX, dexmedetomidine; TGF, tumor growth factor; TNF, tumor necrosis factor; IL, interleukin; ICAM-1, intracellular adhesion molecule. *P<0.01 compared with the control group.*

Compared with the control group, the dexmedetomidine group had significantly decreased C-reactive protein on the first day after operation (36.65±8.05 vs. 54.70±7.21mg.l-1), significantly reduced drainage volume (97.25±23.67

vs. 198.25±36.03 ml) 24 h after the operation, significantly shortened time to get out of bed for the first time (23.60±3.21 vs. 34.17±3.84h), quicker recovery of bowel sounds (61.30±6.04 vs. 85.35±8.38 h), quicker anal exhaust (65.15±6.10 vs. 89.48±8.32 h) and shortened hospital stay (6.58±0.65 vs. 7.85±0.86 d)(P<0.05) (Table 3).

Groups	C-reactive protein (mg.L^{-1})	24-h drainage volume (ml)	First time to get off bed (h)	Bowel sound recovery time (h)	First anal exhaust time (h)	Hospital stay(d)
DEX	36.65±8.05*	97.25±23.67*	23.60±3.21*	61.30±6.04*	65.15±6.10*	6.58±0.65*
Control	54.70±7.21	198.25±36.03	34.17±3.84	85.35±8.38	89.48±8.32	7.85±0.86

Table 3: Comparison of the two groups after operation (mean±standard deviation, n=40 in each group).
*Note: DEX, Dexmedetomidine; *P<0.01 compared with the control group.*

In the dexmedetomidine group, there were 6 patients whose heart rate was lower than 50 bpm, and the heart rate was recovered to more than 60 bpm after 0.5mg atropine was given. In the control group, one patient experiend the heart rate lower than 50 bpm which was recovered to over 60 bpm after administration of atropine 0.5 mg. There were no serious adverse events of bradycardia in both groups. No other side effects or complications occurred in both groups.

ROC curve analysis was performed on indexes with statistical significance (Table 4 and Fig.1-2). All the parameters of the 24-h drainage volume post operation, ICAM-1, TNF-α , IL-6 , C-reactive protein, time to get off bed, bowel sound recovery time, and first anal exhaustion time had high values with the area under the curve (AUC) > 0.9, and the 24-h drainage volume post operation had the highest value (AUC= 1). TGF-β and hospital stay had the moderate value (AUC>0.7).

Variables	AUC	95% CI	P value	Youden index	Sensitivity	Specificity	Cut-off value
TGF- β	0.83	0.74-0.92	0.00	0.55	0.88	0.68	1613.48
ICAM-1	0.91	0.85-0.97	0.00	0.68	0.9	0.78	367.37
TNF-α	0.99	0.98-1.0	0.00	0.9	0.93	0.98	49.5
IL-6	0.97	0.93-1.0	0.00	0.83	0.9	0.93	135.5
C-reactive protein	0.98	0.95-1.00	0.00	0.83	0.85	0.88	46.5
24-h drainage volume	1.00	1.00-1.00	0.00	1.00	1.00	1	145
First time to get out of bed	0.99	0.97-1.00	0.00	0.88	0.95	0.93	28.5
Bowel sound recovery time	0.995	0.99-1.00	0.00	0.93	0.95	0.93	70.5
First anal exhaust time	0.99	0.98-1.00	0.00	0.93	0.83	1	73.5
Hospital stay	0.86	0.77-0.94	0.00	0.60	0.9	0.7	7.5

Table 4: Results of ROC curve analysis of different indexes.
Note: ROC, receiver operating characteristics; AUC, area under the curve; CI, confidence interval; TGF, tumor growth factor; TNF, tumor necrosis factor; IL, interleukin; ICAM-1, intracellular adhesion molecule.

Discussion

In this study investigating the effect of dexmedetomidine on fast recovery and on serum cytokines of TGF-β, ICAM-1, TNF-α, and IL-6 in patients who had selective laparoscopic radical resection of colon cancer, it was found that dexmedetomidine had significantly increased TGF-β but significantly decreased ICAM-1, IL-6, and TNF-α. Moreover, patients with dexmedetomidine application had faster recovery after the operation with significantly reduced drainage volume, quicker recovery of bowel sounds and anal exhaust, shortened time to get out of bed and hospital.

In a systematic review and meta-analysis investigating the effects of dexmedetomidine on perioperative stress, inflammation, and immune function involving 67 studies with 2454 patients in the dexmedetomidine group and 2388 patients in the control group 10, it was found that dexmedetomidine infusion during the perioperative period had inhibited the release of norepinephrine, epinephrine, and cortisol, decreased blood glucose, IL-6, TNF-α, and C-reactive protein, and increased IL-10 in surgical patients. Moreover, the use of dexmedetomidine has also significantly increased the numbers of natural killer cells, B cells, and CD4+ T cells, the ratios of CD4+:CD8+ and Th1:Th2, but decreased CD8+ T-cells. It was thus concluded that dexmedetomidine as an anesthesia adjuvant could attenuate perioperative stress and inflammation and protect the immune function of surgical patients, thus contributing to decreased postoperative complications but improved clinical outcomes. In a study investigating the effect of dexmedetomidine on promoting inflammation resolution of zymosan-induced generalized inflammation in mice[11], it was found that IL - 1β and TNF-α had been inhibited while the anti-inflammatory TGF-β1 had been up-regulated by dexmedetomidine 24 hours after treatment, resulting in attenuation of cytokine storm and acceleration of inflammation resolution. TNF-α has also been reduced while TGF-β increased in other studies investigating the effect of dexmedetomidine on protecting inflammation injury to the body of mice with intracerebral hemorrhage or neuroinflammation in heatstroke[12,13]. In a study investigating the effect of dexmedetomidine on promoting inflammation resolution to improve the lung function in patients undergoing thoracocopic cardiac surgery[14], the inflammatory cytokines TNF-α, IL-6, and ICAM-1 in the dexmedetomidine group were significantly lower than those in the control group after surgery (P < 0.05). In studying the effect of dexmedetomidine on monocyte-endothelial adherence in U937

monocytes and human umbilical vein endothelial cells[15], it was found that dexmedetomidine could attenuate the contents of MCP-1, soluble ICAM-1 and VCAM-1, resulting in decreased monocyte-endothelial adherence. TNF-α and IL-6 have also been revealed to be significantly decreased by the use of dexmedetomidine in patients undergoing laparoscopic hysterectomy[16] or radical resection of ovarian cancer 4. Moreover, the decrease of cytokines of IL-1β, IL-6, TNFα and VEGF-A has been shown to associate with decreased severity of peritoneal adhesion in a post-surgical adhesion mouse model[6], suggesting involvement of these cytokines in the mechanism of peritoneal adhesion formation and use of appropriate substances to decrease these cytokines and subsequent peritoneal adhesion. These studies have proved our outcomes and revealed the mechanism of dexmedetomidine in fast recovery of patients undergoing radical colon resection possibly through its anti-inflammation effect.

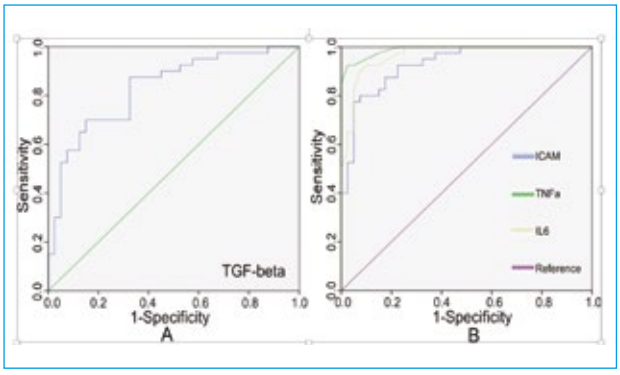

Figure 1: Fig. **A**: Receiver operating characteristics (ROC) curve analysis for TGF-beta, and Fig. ***B***: ROC curve analysis for ICAM, TNF-a, and IL6. TGF, tumor growth factor; TNF, tumor necrosis factor; IL, interleukin; ICAM, intracellular adhesion molecule.

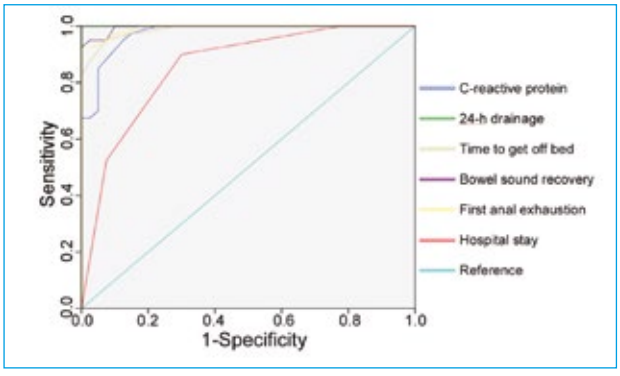

Figure 2: Receiver operating characteristics (ROC) curve analysis for C-reactive protein, 24-h drainage volume, time to get off bed, bowel sound recovery time, first anal exhaustion time, and hospital stay after the procedure.

Compared with the traditional open surgery, laparoscopic radical resection of colon cancer is becoming increasingly popular in clinics because of its less invasiveness and quick recovery. However, pneumoperitoneum and surgical trauma can also affect gastrointestinal function, and the increase of pneumoperitoneum pressure can cause gastrointestinal inflammatory stress response, ischemia-reperfusion injury and postoperative abdominal adhesion. Rapid rehabilitation needs team cooperation, and only changing the operation mode is not enough. Anesthesia also plays an important role, and rational selection of narcotic drugs is conducive to hospital stay. Dexmedetomidine, as a α2-adrenergic receptor agonist, can reduce postoperative pain, nausea, vomiting, and other complications, besides accelerating rapid recovery of patients. Animal experimental studies have shown that dexmedetomidine has an obvious preventive effect on postoperative abdominal adhesion[17], but the clinical effect of dexmedetomidine on the healing of surgical incision anastomosis and abdominal adhesion is still unclear. Our study demonstrated that dexmedetomidine can affect the release of cytokines, thus promoting wound healing and reducing postoperative adhesion.

Intraperitoneal adhesions occur in 93% of patients who have undergone intraabdominal surgery, even though most of these adhesions are asymptomatic[17]. Intraperitoneal adhesions involve formation of fibrin inside the abdominal cavity which is a common pathophysiological event. The peritoneum lines the abdominal cavity and consists of a single layer of mesothelial cells and a sub-mesothelial layer. Abdominal trauma causes mesothelial injury and inflammation, leading to influx of inflammatory cells and fibrinous exudation 18. A fibrous band or bridge will be formed when two peritoneal surfaces covered with fibrous matrix come into contact, and an adhesion will be organized on the band or bridge. Adhesion formation is correlated inversely with the peritoneal fibrinolytic activity, and bacterial peritonitis will decrease the fibrinolytic activity. In case of failed fibrinolytic mechanism, the adhesion will become fibrous and organized, and early balance between fibrin deposition and degradation is the key to prevent adhesion formation[6]. Moreover, the status of peritoneal inflammation may be critical in determining the duration and extent of adhesion, and suppression of the inflammation and promotion of fibrinolytic activity may be a promising strategy for anti-adhesion therapy[19].

Formation of intraperitoneal adhesions results from a complex cascade of interaction which involves humoral and cellular factors, even though the exact mechanism remains unknown. Cellular factors include the mesothelial cells, inflammatory cells, and fibroblasts, whose interplay and the structural organization are adjusted by some cytokines, signaling molecules, and growth factors[20]. The initial local ischemia and subsequently resulted inflammatory reaction in the damaged tissue played a key role in intraperitoneal adhesion formation, and the inflammation is triggered by inflammatory mediators produced by the mesothelial cells from the traumatic area, inducing inflammatory cells to migrate into the traumatic area for adhesion formation.

In the adhesion process, one critical cell is the fibroblast or myofibroblast which releases, upon activation, an increased amount of fibrillar collagens and other matrix proteins[12]. The accumulation of these myofibroblasts and the uncontrolled increased biosynthetic functions are critical for the rate and extent of progression of fibrotic reactions and clinical therapy. As a pleiotropic growth factor with a diverse and wide spectrum of biological functions, TGF-β plays a key role in fibrotic diseases through adjusting formation of myofibroblasts and promoting the production of extracellular matrix[3]. When activated, TGF-β binds to its receptor, a constitutively active serine/threonine transmembrane receptor kinase, and activates some pro-fibrotic pathways[3]. TGF-β is also an important mediator for tissue repair and plays a key role in promoting wound healing through mediating the chemotaxis of inflammatory cells, accelerating the growth of granulation tissue and local microvascular regeneration, and promoting the proliferation and differentiation of fibroblasts, the synthesis and degradation of collagen, elastic fibers and extracellular matrix[22].

TGF-β can affect intestinal adhesion and has an increased expression in the adhesive tissue. The function to promote cellular adhesion of TGF-β may be associated with its ability to increase the vascular endothelial permeability[23], and the use of TGF - β1 receptor inhibitors can reduce the formation of peritoneal adhesion[24]. However, normal level of endogenous TGF - β 1 can inhibit the formation of adhesion, and only overexpression of TGF - β 1 is related to the formation of abdominal adhesion. TGF - β 1 may need to reach twice the normal level to cause tissue adhesion[25]. In our study, the level of TGF-β is still within the normal range and it can only promote tissue repair rather than adhesion.

As a pleiotropic cytokine, IL-6 has a wide extent of biological functions which are achieved through some complex signaling pathways[26]. Acute administration of IL-6 can elevate cellular proliferation and resistance to apoptosis. IL-6 is also found to be capable of driving a peritoneal fibrotic process[273]. It can promote epithelial or mesothelial to mesenchymal cell transition which may be an important cellular mechanism for intraperitoneal adhesions because of its ability to be a source of myofibroblasts. In local tissues, IL-6 is mainly produced by fibroblasts or local macrophages. As a proinflammatory cytokine, IL-6 plays an important role in the process of inflammation. IL-6 and TGF-β are increased in the peritoneal fluid of patients who had undergone abdominal surgery, and the levels of the cytokines are related to the severity of intraperitoneal adhesion formation[28].

As a transmembrane glycoprotein on the cell surface, ICAM-1 is the main member of immunoglobulin superfamily in adhesion molecules and can mediate the interaction between cells or between cells and extracellular matrix[29]. It can stimulate the infiltration of inflammatory cells in wound, affect the speed of wound recovery, mediate adhesion reaction, and participate in tissue fibrosis. ICAM-1 can activate T cells in vascular endothelial cells by promoting cell adhesion. Application of dexmedetomidine can alleviate ischemia-reperfusion damage to the rat brains by inhibiting the expression of NK-kB and ICAM-1 in the oxidative stress and inflammatory responses[7]. Decrease of the expression of ICAM-1 can reduce the tissue ischemia-reperfusion injury, resulting in an organ protective effect[30]. In our study of laparoscopic radical resection of colon cancer, pneumoperitoneum will inevitably cause intestinal ischemia-reperfusion injury, and the low level of ICAM-1 in the dexmedetomidine group was beneficial to intestinal protection and postoperative intestinal function recovery.

Tissue will release a lot of inflammatory factors after being stimulated by traumatic pain. TNF - α is a monocyte factor, which is mainly produced by monocyte macrophages in vivo. It has a variety of biological activities and biological effects, and plays an important role in inflammatory reaction. Decrease of TNF - α is beneficial to wound healing, while increase of TNF - α can delay the process of skin wound healing[31]. TNF - α can also induce endothelial cell adhesion and mediate adhesion after abdominal surgery[5]. Continuous use of

dexmedetomidine during the general anesthesia can effectively reduce the perioperative serum levels of TNF - α and IL-6, and inhibit the stress response, and this effect can last for more than 3 days 4. In our study, the use of dexmedetomidine decreased the serum level of TNF-α and IL-6, possibly reducing formation of postoperative intraperitoneal adhesions. Significant decrease in the inflammation cytokines of TNF-α and IL-6 has been demonstrated by the use of dexmedetomidine in patients undergoing laparoscopic hysterectomy 16 or radical resection of ovarian cancer 4, and the decrease of cytokines of IL-1β, IL-6, TNFα and VEGF-A has been shown to associate with decreased severity of peritoneal adhesion in a post-surgical adhesion mouse model 6, which supported our study.

Some limitations existed in this study including a small cohort of patients, one single center study, and Chinese patients enrolled only, which may all possibly produce some outcome bias and affect the generalization of the outcome. Better results can be achieved without significant bias by using a large cohort of patients, multiple research centers, multiple races of people, and double-blinded design in an international clinical trial. Future randomized controlled clinical trials involving more patients, multiple medical centers, and multiple races will have to be performed to resolve these issues for better outcomes.

In conclusion, dexmedetomidine can promote the healing of surgical wound and reduce the occurrence of postoperative adhesion by regulating the expression of cytokines, which is conducive to the rapid recovery of patients with colon cancer.

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