European Review for Medical and Pharmacological Sciences 2018; 22: 3570-3576

Cardiocerebral protective effects of dexmedetomidine as anesthetic in colorectal cancer surgery

X.-L. YI[1], J.-T. WANG[1], C.-Q. CHU[1], Y.-X. LI[2], J.-H. YIN[1], S.-L. LIU[3]

[1]Department of Anesthesiology, The Affiliated Hospital of Qingdao University, Qingdao, P.R. China
[2]Yuhuangding Hospital of Yantai, Yantai, P.R. China
[3]Department of Ultrasonography, The Affiliated Hospital of Qingdao University, Qingdao, P.R. China

Xuanlong Yi and Juntao Wang contributed equally to this study

Abstract. – OBJECTIVE: To explore the cardiocerebral protective effect of dexmedetomidine as an anesthetic in colorectal cancer surgery.

PATIENTS AND METHODS: A total of 246 colorectal cancer patients were enrolled in this retrospective analysis. Those patients were admitted to the Affiliated Hospital of Qingdao University and underwent surgery from July 2014 to July 2016. The patients were divided into observation group and control group according to the anesthetic used in surgery. The conventional anesthetic was administered to patients in control group, whereas conventional anesthetic supplemented with dexmedetomidine was administered to patients in the observation group. The heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), jugular venous oxygen saturation (Sj-vO_2), cerebral oxygen extraction ratio (ERO2), and cerebral arterial partial pressure of oxygen (PaO_2) were recorded before dexmedetomidine administration (T0), 30 min after start of surgery (T1), and 2 h after surgery (T2). Central venous blood (4 ml) was withdrawn 6 hours and 24 hours after surgery. Following centrifugation, the serum was collected and stored at -70°C. After collection of all the blood samples, concentrations of creatine kinase (CK-MB), troponin I (cTnI), TNF-α and S100β in serum were measured using ELISA, and differences between the two groups were compared.

RESULTS: Differences of the parameters measured at T0 were not statistically significant between observation group and control group ($p>0.05$), whereas the parameters measured at T1 and T2 were significantly better in the observation group than those in the control group ($p<0.05$). The post-surgery blood test showed that indicators of cardiocerebral hemodynamics were better in the observation group than those in the control group ($p<0.05$).

CONCLUSIONS: Administration of dexmedetomidine in colorectal cancer surgery can provide effective cardiocerebral protection and it is worth popularizing in clinical practice.

Key Words:
Dexmedetomidine, Colorectal cancer, Surgery, Anesthesia, Cardiocerebral function.

Introduction

The colorectal resection is currently the common treatment of patients with colon cancer. With the continuous progress of medical devices, the colorectal resection surgery has matured. However, the success rate of surgery is closely related to perioperative cardiocerebral protection[1-3]. Surgical operation triggers stress responses of patients with colon cancer in the perioperative period, resulting in hemodynamic abnormalities. These abnormalities often lead to cardiocerebral damage due to the insufficient blood supply to the heart and an imbalance between oxygen demand and supply in the heart[4,5]. Preoperative anesthesia may also trigger systemic inflammatory response syndrome. The activation of the complement proteins C3 and C4, as well as monocytes, and the increased levels of inflammatory cytokines such as TNF and interleukins-6 all play important roles[6,7]. Different degrees of ischemia, hypoxia, and inflammatory reactions that may occur in colon cancer surgery are the main causes of cardiocerebral damage[8,9].

Dexmedetomidine is commonly used as anesthetic, sedative, and analgesic in clinical treatments[10]. Dexmedetomidine activates α2 adrenergic receptor with high affinity and inhibits the release of norepinephrine so as to relieve or even inhibit the stress response induced by surgical stimulation, improve perioperative hemodynamics, maintain cardiac oxygen supply-demand balance,

Corresponding Author: Suli Liu, MD; e-mail: aps4ey@163.com

and reduce expression levels of cytokines associated with a brain injury like S100β[11,12].

In this study, the cardiocerebral protective effect of dexmedetomidine during perioperative period was explored by the intravenous drip of dexmedetomidine following induction of conventional anesthesia during colon cancer surgery.

Patients and Methods

Patients

A total of 246 patients with colorectal cancer were enrolled in this retrospective analysis, who were admitted to the Affiliated Hospital of Qingdao University and underwent surgery from July 2014 to July 2016. The enrolled patients were aged 35 to 55 years, weighed 45 to 75 kg, and were assigned to class II and class III in the ASA classification system. Depending on whether dexmedetomidine was administered in surgery, patients were divided into observation group (n=126) and control group (n=120). Patients in observation group received conventional anesthesia supplemented with dexmedetomidine, whereas patients in control group received conventional anesthesia and normal saline. Inclusion criteria: patients underwent initial surgery; patients showed no allergic to dexmedetomidine; patients without liver, kidney, and other organ dysfunction; patients without abnormal bleeding or coagulation disorders. Exclusion criteria: patients with cardiovascular disease; patients with excessive lumps; patients with other lung or chest wall disease; patients with lymph node metastasis. All patients or their families signed the informed consent. The study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University.

Treatment Methods

Anesthesia was induced by intravenous injection of etomidate 0.3 mg/kg, midazolam 0.05 mg/kg, rocuronium 0.6 mg/kg, and sufentanil 1 μg/kg for all patients. After anesthetic induction, patients in the observation group were further given an intravenous injection of dexmedetomidine 0.5 μg/kg within 15 min, followed by continuous IV drip at a rate of 0.5 μg/kg/h until the end of surgery. Patients in the control group received intravenous saline drip at a rate of 0.5 μg/kg/h. Anesthesia was maintained by inhalation of aerosolized sevoflurane (1.5%) and intravenous infusion of sufentanil via infusion pump at a rate of 0.6 μg/kg/h. The Bispectral Index value was maintained between 45 and 65.

ELISA Measurement of Serum Proteins

The concentrations of CK-MB, cTnI, TNF-α, and S100β in serum were measured with ELISA according to instructions of the ELISA kit (Shanghai Enzyme Research Biotechnology Co., Ltd., Shanghai, China). Serum samples from all patients were collected and stored at -70°C. Reagents and standards were prepared, and standard curves were plotted. The OD values were measured at 450 nm.

Observed Indicators

Five indicators of brain function including ERO_2, PaO_2, Sj-vO_2, TNF-α, and S100β, as well as five indicators of cardiac function including HR, SBP, DBP, CK-MB, and cTnI, were acquired at three time points, i.e., before dexmedetomidine administration (T0), 30 min after start of surgery (T1), and 2 h after surgery (T2).

Statistical Analysis

Statistical software SPSS 19.0 (AsiaAnalytics, formerly SPSS China) was used in data processing. The Chi-squared X^2-test was used for the comparison of rate. Normal distribution measurement data were expressed as ±s and compared using Student's *t*-test. The non-parametric K-S test was used for comparison of non-normal distribution measurement data between groups. The difference was statistically significant if $p<0.05$.

Results

Clinical Records

246 patients with colorectal cancer were divided into two groups. Among 126 patients in the observation group, 69 were males and 57 were females. The mean age was 48.6±12.3 years in this group. Among 120 patients in the control group, 72 were males and 48 were females. The mean age was 44.7±9.6 years in this group. There were no significant differences in general medical information between patients in the two groups such as gender, body weight, and age ($p>0.05$). The detailed patient information are shown in Table I.

Cardiac Function Evaluation

There were no significant differences in HR, SBP, and DBP between the two groups at T0 ($p>0.05$). The levels of HR, SBP, and DBP in the observation group were significantly better than those in the control group at T1 and T2 ($p<0.05$). The ELISA results showed that the CK-MB and

Table I. General medical information of patients in the two groups.

Item		Control group	Observation group	*p*-value
Patient number		120	126	0.142
Male/female		72/48	69/57	0.589
Hemoglobin before surgery (g/dl)		9.52±1.34	9.67±1.44	0.399
Albumin before surgery (g/dl)		3.54±0.56	3.49±0.48	0.452
Surgical approach			0.954	
	Open surgery	36 (30.00)	38 (30.16)	
	Minimally invasive surgery	84 (70.00)	88 (69.84)	
Amount of blood transfusion (ml)		165.32±13.25	168.33±13.14	0.074
Liquid input in 6 h (ml)		1320.21±100.52	1336.12±101.34	0.218
Liquid input in 24 h (ml)		1103.49±87.64	1084.57±91.27	0.099
Eyes open time		15.23±2.38	11.74±2.38	<0.001
Operation time (min)		184.63±9.25	186.94±9.27	0.052
Age (years)		44.7±9.6	48.6±12.3	0.736
Body weight, n (%)	<50 kg	54 (45.00)	52 (41.27)	0.969
	≥50 kg	66 (55.00)	74 (58.73)	
Smoking history, n (%)	Yes	33 (27.50)	29 (23.02)	0.565
	No	87 (72.50)	97 (76.98)	
Residence, n (%)	Urban area	81 (67.50)	72(57.14)	0.381
	Rural area	39 (32.50)	54 (42.86)	
Colon/rectal cancer, n (%)	Colon cancer	58 (48.33)	66 (52.38)	0.715
	Rectal cancer	62 (51.67)	60 (47.62)	

Table II. Indicators of cardiac function of patients in the two groups.

Indicator	Time point	Control group	Observation group	*p*-value
HR	T0	66.8±11.8	65.9±12.7	0.732
	T1	86.1±10.5	66.8±11.1	0.032
	T2	99.4±12.2	87.5±11.5	0.045
SBP	T0	119.6±13.8	130.9±12.4	0.783
	T1	103.1±14.8	114.5±15.6	0.039
	T2	97.2±7.1	104.2±9.8	0.046
DBP	T0	65.6±11.6	65.4±12.5	0.975
	T1	58.8±8.2	62.1±9.1	0.028
	T2	55.4±6.1	64.5±7.2	0.031

Table III. Indicators of brain function of patients in the two groups.

Indicator	Time point	Control group	Observation group	*p*-value
ERO_2	T0	39.2±6.4	37.4±8.8	0.547
	T1	26.4±8.1	19.6±9.4	0.024
	T2	35.5±7.6	27.4±7.7	0.031
PaO_2	T0	131.9±58.2	134.2±66.5	0.786
	T1	213.5±33.7	234.5±47.9	0.042
	T2	187.3±37.2	214.3±44.7	0.034
Sj-vO_2	T0	64.7±6.9	67.2±8.1	0.832
	T1	59.6±6.5	73.6±7.6	0.032
	T2	61.7±7.6	69.2±8.1	0.044

cTnI levels in the observation group were lower than those in the control group 6 hours and 24 hours after surgery ($p<0.05$). The data are shown in Table II, Figure 1 and Figure 2.

Brain Function Evaluation

There were no significant differences in ERO_2, PaO_2, and Sj-vO_2 between the two groups at T0 ($p>0.05$). The levels of ERO_2, PaO_2, and Sj-vO_2 in the observation group were significantly better than those in the control group at T1 and T2

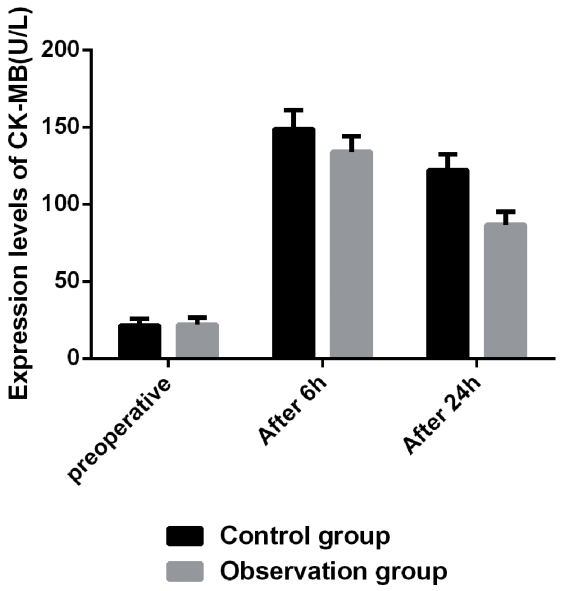

Figure 1. Expression levels of CK-MB. ELISA showed that CK-MB levels 6 h and 24 h after surgery was lower in the observation group than those in the control group (p=0.032, p=0.013).

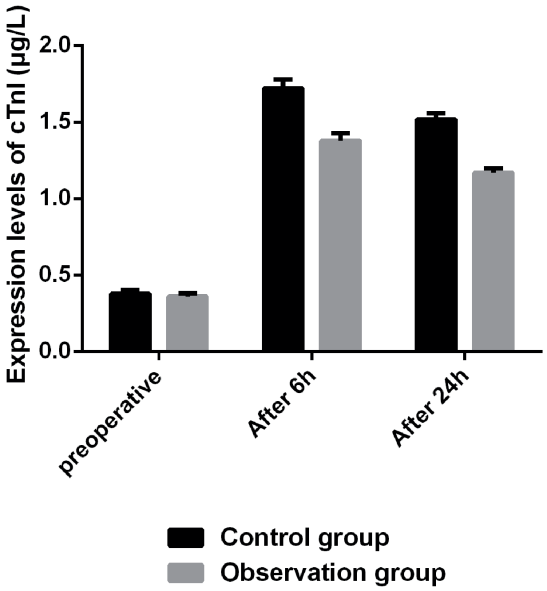

Figure 2. Expression levels of cTnI. ELISA showed that cTnI levels 6 h and 24 h after surgery was lower in the observation group than those in the control group (p=0.014, p=0.025).

(p<0.05). The ELISA results showed that levels of TNF-α and S100β in the observation group were lower than those in the control group 6h and 24h after surgery (p<0.05). The data are shown in Table III, Figure 3 and Figure 4.

Discussion

Colorectal cancer occurs more often in middle-aged males. Its pathogenesis is not yet well understood and its prognosis is closely related to early diagnosis and surgical treatment[13,14]. However, cardiocerebral damage may result from surgery due to traumatic stimulation and hemodynamic abnormalities during surgery[15,16]. Dexmedetomidine was effective in attenuating stress response to surgical stimulation and improving the oxygen supply-demand balance in the heart[17,18]. In this study, the perioperative cardiocerebral protective effect of dexmedetomidine was explored by an intravenous drip of dexmedetomidine following induction of conventional anesthesia during colon cancer surgery.

Retrospective analysis of medical records of 246 patients with colorectal cancer undergoing colorectal resection was performed. It was found that the intraoperative and postoperative levels of HR, SBP, and DBP were all better in patients who received dexmedetomidine than in patients who did not receive dexmedetomidine during surgery. In addition, the ELISA results showed that levels of CK-MB and cTnI were decreased 6 h and 24 h after surgery in patients who received dexmedetomidine. Thus, dexmedetomidine was effective in maintaining SBP, DBP, and HR of patients

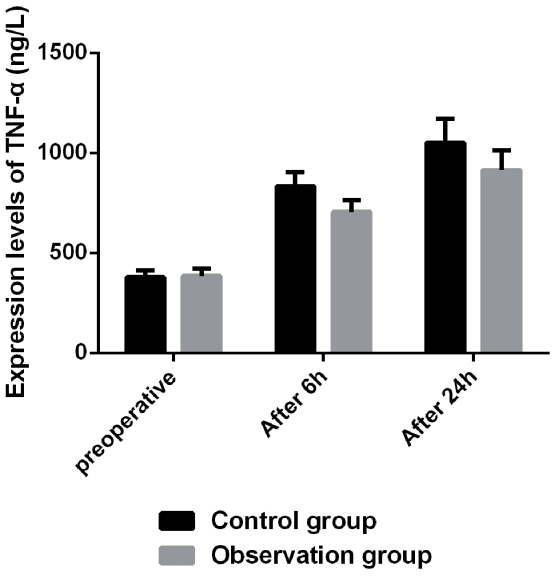

Figure 3. Expression levels of TNF-α. ELISA showed that TNF-α levels 6 h and 24 h after surgery was lower in the observation group than those in the control group (p=0.028, p=0.031).

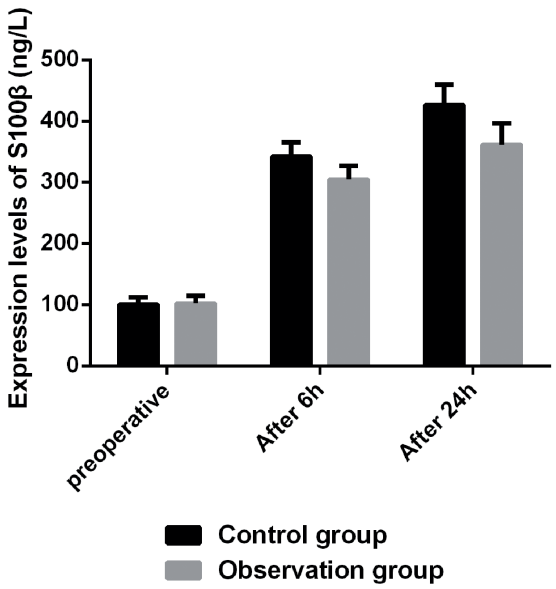

Figure 4. Expression levels of S100β. ELISA showed that S100β levels 6 h and 24 h after surgery was lower in the observation group than those in the control group (p=0.037, p=0.029).

during surgery and protecting cardiac function. A lot of researchers confirmed the positive effect of dexmedetomidine on hemodynamic stability during surgical treatment of cerebrovascular malformation[19]. Also, Ammar et al[20] reported that dexmedetomidine could reduce levels of cardiac-specific proteins in serum such as troponin-I and creatine kinase-MB during cardiac surgery, alleviate cardiac damage due to surgical stimulation and improve cardiac function. In another study, Lee et al[21] reported that dexmedetomidine inhibited stress response to surgery and maintained hemodynamic stability during laryngoscope and tracheal intubation. These findings in the literature mentioned above were in accordance with findings in this study, which demonstrated perioperative protective effects of dexmedetomidine on cardiac function during surgery of multiple conditions. Studies have found that cardiac output and systemic vascular resistance are more accurate in assessing hemodynamics. This is a flaw in our experimental design, so there is a certain deviation in the evaluation of cardiac function in patients. We will improve the experimental design in our future investigations.

We also found that the intraoperative and postoperative levels of ERO_2, PaO_2, and Sj-vO_2 were all better in patients who received dexmedetomidine than in patients who did not receive dexmedetomidine during surgery. In addition, the ELISA results showed that levels of TNF-α and S100β were decreased 6 h and 24 h after surgery in patients who received dexmedetomidine. Thus, dexmedetomidine was effective in maintaining Sj-vO_2 and ERO_2 of patients during surgery and protecting cerebral function. TNF-α is a pro-inflammatory cytokine, and S100β is a brain-specific protein. Brain damage can be evaluated by monitoring level changes of these two proteins in patients[22]. In recent years, an upward trend in incidence and mortality of cerebrovascular diseases[23,24] has warranted more studies on cerebral protective effects of dexmedetomidine. Li et al[25] reported that dexmedetomidine attenuated cerebral damage due to ischemia-reperfusion, by inhibiting expression of NF-κB and cell adhesion molecule-1 associated with oxidative stress and inflammatory reaction in brain tissue. We found that dexmedetomidine played a protective role in the brain by reducing the expression of inflammatory cytokine TNF-α. In another study, Ding et al[26] reported that dexmedetomidine shortened the recovery time from anesthesia in elderly patients undergoing radical cystectomy, and improved patient's postoperative cognitive function. Also, Zhao et al[27] found that dexmedetomidine was effective in maintaining cerebrovascular hemodynamic stability, thus avoided respiratory depression, and protected the brain from damage.

The current work is a retrospective analysis with a small sample size. Nevertheless, considering that dexmedetomidine was effective in inhibiting stress response and inflammatory reaction induced by surgical stimulation, promoting hemodynamic stability and cerebral oxygen consumption, further larger studies are needed to validate those results.

Conclusions

We showed that dexmedetomidine was effective in inhibiting stress response and inflammatory reaction induced by surgical stimulation and maintaining hemodynamic stability and cerebral oxygen consumption. Thus, dexmedetomidine has cardiocerebral protective effects.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University. Signed written informed consents were obtained from the patients and/or guardians.

Conflict of Interest

The Authors declare that they have no conflict of interest.

References

1) Van der Pas MH, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC, Bonjer HJ. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 2013; 14: 210-218.
2) Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, , Jaeck D, Mirza D, Parks RW, Collette L, Praet M, Bethe U, Van Cutsem E, Scheithauer W, Gruenberger T; EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK; Arbeitsgruppe Lebermetastasen und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); Australasian Gastro-Intestinal Trials Group (AGITG); Fédération Francophone de Cancérologie Digestive (FFCD). Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013; 14: 1208-1215.
3) Green BL, Marshall HC, Collinson F, Quirke P, Guillou P, Jayne DG, Brown JM. Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. Br J Surg 2013; 100: 75-82.
4) Artinyan A, Orcutt ST, Anaya DA, Richardson P, Chen GJ, Berger DH. Infectious postoperative complications decrease long-term survival in patients undergoing curative surgery for colorectal cancer: a study of 12,075 patients. Ann Surg 2015; 261: 497-505.
5) Malietzis G, Giacometti M, Askari A, Nachiappan S, Kennedy RH, Faiz OD, Aziz O, Jenkins JT. A preoperative neutrophil to lymphocyte ratio of 3 predicts disease-free survival after curative elective colorectal cancer surgery. Ann Surg 2014; 260: 287-292.
6) Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. Ann Surg 2014; 259: 916-923.
7) Reisinger KW, van Vugt JL, Tegels JJ, Snijders C, Hulsewé KW, Hoofwijk AG, Stoot JH, Von Meyenfeldt MF, Beets GL, Derikx JP, Poeze M. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. Ann Surg 2015; 261: 345-352.
8) Reinert T, Schøler LV, Thomsen R, Tobiasen H, Vang S, Nordentoft I, Lamy P, Kannerup AS, Mortensen FV, Stribolt K, Hamilton-Dutoit S, Nielsen HJ, Laurberg S, Pallisgaard N, Pedersen JS, Ørntoft TF, Andersen CL. Analysis of circulating tumour DNA to monitor disease burden following colorectal cancer surgery. Gut 2016; 65: 625-634.
9) Kennedy RH, Francis EA, Wharton R, Blazeby JM, Quirke P, West NP, Dutton SJ. Multicenter randomized controlled trial of conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme: EnROL. J Clin Oncol 2014; 32: 1804-1811.
10) Diao HX, Jiang S, Gao PY, Liu HY, Li JN, Fan HG. Abstract PR363: Comparison of the effects of dexmedetomidine-isoflurane and isoflurane anesthesia on brain injury after cardiac valve replacement surgery. Vet Anaesth Analg 2016; 43: 145-152.
11) Hayes BD, Nelson LS. Letter in response to evaluation of early dexmedetomidine addition to the standard of care for severe alcohol withdrawal in the ICU: a retrospective controlled cohort study. J Intensive Care Med 2016; 31: 353-354.
12) Balkanay OO, Goksedef D, Omeroglu SN, Ipek G. The dose-related effects of dexmedetomidine on renal functions and serum neutrophil gelatinase-associated lipocalin values after coronary artery bypass grafting: a randomized, triple-blind, placebo-controlled study. Interact Cardiovasc Thorac Surg 2015; 20: 209-214.
13) Li C, Carli F, Lee L, Charlebois P, Stein B, Liberman AS, Kaneva P, Augustin B, Wongyingsinn M, Gamsa A, Kim DJ, Vassiliou MC, Feldman LS. Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. Surg Endos 2013; 27: 1072-1082.
14) Souverijn JH. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014; 370: 1287-1297.
15) Luo C, Liang F, Ren H, Yao X, Liu Q, Li M, Qin D, Yuan TF, Pei Z, Su H. Collateral blood flow in different cerebrovascular hierarchy provides endogenous protection in cerebral ischemia. Brain Pathol 2017; 27: 809-821.
16) Hasegawa Y, Nakagawa T, Matsui K, Kim-Mitsuyama S. Renal denervation in the acute phase of ischemic stroke provides brain protection in hypertensive rats. Stroke 2017; 48: 1104-1107.
17) Yu M, Han C, Jiang X, Wu X, Yu L, Ding Z. Effect and placental transfer of dexmedetomidine during caesarean section under general anaesthesia. Basic Clin Pharmacol Toxicol 2015; 117: 204-208.
18) Han C, Jiang X, Wu X, Ding Z. Application of dexmedetomidine combined with ropivacaine in the cesarean section under epidural anesthesia. Zhonghua Yi Xue Za Zhi 2014; 94: 3501-3505.
19) Kang WS, Kim SY, Son JC, Kim JD, Muhammad HB, Kim SH, Yoon TG, Kim TY. The effect of dexmedetomidine on the adjuvant propofolrequirement and intraoperative hemodynamics during remifentanil-based anesthesia. Korean J Anesthesiol 2012; 62: 113-118.
20) Ammar AS, Mahmoud KM, Kasemy ZA, Helwa MA. Cardiac and renal protective effects of dexmedetomidine in cardiac surgeries: a randomized controlled trial. Saudi J Anaesth 2016; 10: 395-401.

21) Lee JH, Kim H, Kim HT, Kim MH, Cho K, Lim SH, Lee KM, Kim YJ, Shin CM. Comparison of dexmedetomidine and remifentanil for attenuation of hemodynamic responses to laryngoscopy and tracheal intubation. Korean J Anesthesiol 2012; 63: 124-129.

22) Çanakçı E, Özmen SA, Çolak MF, KürĐad H. Histopathologic comparison of dexmedetomidine's and thiopental's cerebral protective effects on focal cerebral ischemia in rats. Rev Bras Anestesiol 2016; 66: 583-593.

23) Sepehripour AH, Athanasiou T. Developments in surgical revascularization to achieve improved morbidity and mortality. Exp Rev Cardiovasc Ther 2016; 14: 367–379.

24) Schokker SA, Van Oostwaard MF, Melman EM, Van Kessel JP, Baharoglu MI, Roos YB, Vogt L, De Winter RJ, Mol BW, Ganzevoort W. Cerebrovascular, cardiovascular and renal hypertensive disease after hypertensive disorders of pregnancy. Pregnancy Hypertens 2015; 5: 287-293.

25) Liu JJ, Pan SY. Protective effects of estrogen combined with sevoflurane in an experimental model of cerebral infarction and focal cerebral ischemia-reperfusion injury. Eur Rev Med Pharmacol Sci 2016; 20: 1839-1844.

26) Ding L, Zhang H, Mi W, Wang T, He Y, Zhang X, Ma X, Li H. Effects of dexmedetomidine on anesthesia recovery period and postoperative cognitive function of patients after robot-assisted laparoscopic radical cystectomy. Int J Clin Exp Med 2015; 8: 11388-11395.

27) Zhao J, Zhou C. The protective and hemodynamic effects of dexmedetomidine on hypertensive cerebral hemorrhage patients in the perioperative period. Exp Ther Med 2016; 12: 2903-2908.