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Research Article

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Effect of Entropy Index-Targeted Dextromeetomidine on Postoperative Neurocognitive Function in Elderly Patients with Gastrointestinal Tumors

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Abstract

Objective: *To investigate the effect of entropy index targeted monitoring combined with dexmedetomidine infusion on cognitive function after thoracic and abdominal surgery in elderly patients.*

Methods: *60 elderly patients undergoing abdominal surgery in our hospital on October ~2017 and October 2019 were selected, ASAII~ grade III, and the random digital table method was divided into 3 groups ,20 cases in each group. entropy index monitoring combined with dexmedetomidine group (D1 group), entropy index monitoring combined with dexmedetomidine group (D2 group) and dexmedetomidine monitoring combined with saline group (D0 group). All patients were subjected to sequential rapid induction of endotracheal intubation general anesthesia. D1, D2, the group was injected with 0.5μg/kg dexmedetomidine hydrochloride intravenously in the first 15 min of induction, followed by a 0.3μg•kg-1•h-1, 0.6μg•kg-1•h-1 maintenance pump until 30 minutes before the end of operation, respectively. The D0 group was injected with the same amount of saline intravenously before induction, and then maintained with the same amount of saline. D1 and D2 groups were calibrated at 40~60. preoperative (T1), tracheal intubation immediate (T2),30 min after operation (T3) and extubation immediate (T4) M after operation were compared in 3 groups AP (mmhg), hr (sub/ min), blood oxygen saturation (SpO2) and intraoperative anesthetic dosage, vasoactive drug use, and postoperative recovery status; simple intelligent mental state examination scale (MMSE) test was completed 1 day before ,1 day after ,3 days after and 7 days after operation to record the incidence of perioperative neurocognitive disorders (PND). To detect the necrosis factor-α(TNF-α) and C-reactive protein (CRP) of the above-mentioned concurrent serum tumors; Results Compared with D0 group, the MAP of D1 group and D2 group decreased significantly and the HR slowed down significantly (P<0.05), The MAP, HR of T3, T4 in D2 group was significantly decreased compared with that in the D1 group (P<0.05), but the difference was not significant at all time points (0.05);The respiratory recovery time (min), dialling time (min) and restoring directional force time (min) were significantly shortened compared with the D0 group and the D2 group, and the consumption of propofol and sufentanil during the operation was significantly decreased. Compared with the D2 group, the use of vasoactive drugs in the D1 group was significantly decreased (P<0.05). The TNF-α, CRP of patients in the first day and the third day were higher than those in the first day of operation, but the TNF-α, CRP of D1 group and D2 group were lower than those in the D0 group (0.05). The MMSE scores of l days and 3 days after operation in D1 and D2 groups were higher than those in D0 groups. Significantly decreased (P<0.05), and there was no significant difference between the groups 7 days after operation (P>0.05): Conclusion entropy index targeted monitoring combined with dexmedetomidine infusion (0.3μg/kg/h) in the elderly patients during surgery can improve the intraoperative and postoperative hemodynamic stability, can improve the perioperative neurocognitive disorders of patients, worthy of clinical promotion.*

Keywords: Entropy Index; Dexmedetomidine; Elderly Patients; Perioperative Neurocognitive Disorders

Perioperative neurocognitive impairment perioperative neurocognitive disorders, PND) is a postoperative condition characterized by neurocognitive deficits, and animal and human studies suggest that neuroinflammation caused by surgery or anesthesia is the main cause of PND [1]. The main neurocognitive impairment (PND) after surgical anesthesia are mainly postoperative delirium (s, POD) and postoperative cognitive dysfunction (postoperative cognitive dysfunction, POCD).

The Katarzyna Czyz-Szypenbejl team study showed that postoperative PND occurs in 20% to 50% of patients, with higher prevalence in older patients, cardiovascular disease and heart failure [2]. Older age is considered as an independent risk factor for PND.PND is associated with poor postoperative conversion, resulting in prolonged hospitalization, rehospitalization rate, and increased patient mortality. There is no effective treatment for PND, and the reason for the increased risk of PND in older patients is unknown. Age and type of surgery have been identified as difficult to change risk factors, and anesthesia management is a potentially modifiable risk factor for PND [3].

The specific pathogenesis of PND is currently unknown, and it is believed to be related to the neuroinflammatory response, and the application of dexmetomidine can reduce brain injury in general anaesthetic surgery. However, the ideal administration method of dexmetomidine is not unified and may increase the hypotension and deepen the anesthesia depth with the increase of the dose, which does not benefit the patient's recovery [4]. Enropy index monitoring of the consciousness level of patients with general anesthesia or deep sedation is a new method of EEG monitoring. Response entropy (RE) and state entropy (SE) in entropy represent EM and EEG states, respectively, and reaction entropy can display EEG information more timely and quickly; the combination is rarely reported in the literature.

In this study, the effects of different doses of dexmetomidine on cognitive function after general anesthesia were evaluated by titrating the entropy index targeted index and combining with changes in perioperative serum tumor necrosis factor- (TNF-) and C-reactive protein (CRP) levels in elderly patients with gastrointestinal tumor surgery.

Data and Methods

General Data This study is a prospective, interventional cohort study. The study protocol was approved by the Ethics Committee of Hefei Eighth People's Hospital (ethical batch number: 201706; China Clinical Trial Registration Center Record number: EC-20200324-1019), and all patients signed the informed consent. Elderly patients who underwent gastrointestinal tumor surgery from October 2017 to October 2019 from Hefei Eighth Hospital were selected as the study subjects. Inclusion criteria: ① age 65 years; ② patients are normally conscious, can read and communicate clearly; ③ American Association of Anesthesiologists (ASA) grade ~; ④ elective gastrointestinal tumor surgery. Exclusion criteria: ① preoperative Simple Intelligence Scale (MMSE) score <25; ② allergic to DM and its components; ③ diabetes; ④ hypertension; severe ⑤ heart block, slow sinus movement; ⑥ positional hypotension with recent sedative agents, immunosuppressors and antidepressants; ⑦ preoperative hematocrit <30%, hemoglobin <100g/L; ⑧BMI≤18 kg/m2 or BMI 30 kg / m^2; ⑨ surgery for less than 2 hours or over 4 hours. Excluding criteria: major ① complications (intraoperative or postoperative cerebral infarction, postoperative pulmonary lectasis, anastomotic fistula, etc.), ② postoperative follow-up interruption (postoperative death and refusal to participate in the trial); reoperation within 7 days after ③; ④ bleeding over 400 ml.

Group processing was randomly assigned by a professional staff preparing coding and sealing opaque envelope, with a ratio of 1:1. According to the intraoperative infusion dose, patients were randomly divided into the following three groups: Group 1 (D1) was intravenous pumped into dexidine hydrochloride for 15min with a dose of 0.5 g kg^{-1}, Concentration of 4 u g/ml; followed by 0.3 g kg-1•h^{-1}(Concentration of 4 u g/ml) was maintained until the peritoneal suture was completed, and the second group (group D2) first pumped the induction volume for 15min in the same method in group D1, followed by 0.6 g kg-1•h^{-1} (Concentration of 8 u g/ml) was maintained. The third (D0) D0 group pumped equal amounts of saline 15 min before cannulation and was subsequently maintained with equal amounts of saline. The dedicated anesthesia nurse was responsible for the preparation and infusion of dexmetomidine. The anesthesiologist is responsible for reaction entropy (Reaction Entropy, RE) monitoring, with all three calibrated RE target values of 40 to 60; increase propofol infusion dose (one gradient in T C I 0.2 u g/ml) until the RE is less than 40, reduce propofol infusion dose (one gradient in TCI 0.2ug / ml). Three groups had targeted infusion of sulfentanyl (maintenance effector compartment concentration of 0.3 ng/ml) and intermittent injection of acraconium cisene sulfonate.

Anesthesia method Open the right internal jugular vein after home invasion with an infusion of 37.0°C Ringer's fluid for 5 ml/kg. Multi-kinetic energy monitor monitors reaction entropy (Entropy Spectropy monitor, GM, model B40i), ECG, Sp02And, PETC02, the radial artery was inserted to measure the internal arterial pressure. All patients used sequential rapid induction of endotracheal intubation entirely by intravenous anesthesia, intraoperative mechanical ventilation, and respiratory parameters to maintain PETC02At 35 to 45 m m H g. The procedure was performed by the same group of experienced physicians, and anesthesia was induced and maintained by the same group who did not know the grouping; intraoperative data collection and postoperative follow-up was completed by the two anesthesiologists without the grouping independently. Patient vital signs were closely monitored when BP decreased > 20% or absolute less than 90 mmHg with 6mg of ephedrine until BP returned to baseline or at least over 90 mmHg and 0.5mg at HR <45 / min until 60 times / min.Maintain a nasopharyngeal temperature ranging from 36.0 to 37.0°C Postoperative analgesia was performed with a 100ml analgesic pump (2.0 m l / h) / kg l sulfenthanil / kg flubifenide, followed by the anesthesia nurse and the test was interrupted when the VAS score was greater than 7.

① main indicators: l days before surgery, l, 3 and 7 days after surgery were measured using MMSE scale. The test was independently completed by two (trained) professionals, including directional force, memory, language ability, execution ability and calculation ability. The total score was 30, score <24 indicates the presence of PND, and the postoperative score was more than 1 point lower than before surgery, PND can also be considered to be occurring and record the incidence of PND in each group [4]. ② secondary indicators: electrochemiluminescence to detect simultaneous serum tumor necrosis factor- (TNF-), C-reactive protein (CRP); record 3 patients before surgery (T1) (T2) immediately after DM injection, 30min (T3) (time point best related to dextroadministration, not surgery related) and 60min (T4) MAP (mmHg), HR (sub / minute), oxygen saturation (SpO2); ③ recorded the amount of anesthetic (propofol) and the recovery of surgery.

Statistical analysis was performed using the SPSS 23.0 statistical software. Normal distributed measurement data are expressed as mean standard deviation of ± (x ± s); one-way ANOVA and Bonferroni test are used for group question comparison, ANOVA designed with repeated measurement design and count data2checkout.P <0.05 was considered as a statistically significant difference.

Bear Fruit

1. Trial Completion: 72 patients, 5 massive bleeding, 3 secondary surgery, 1 death, 3 interrupted follow-up, and finally a total of 60 patients com pleted the trial, 20 patients in each group.
2. Baseline data: general comparison of patients: average age, gender composition, BMI, ASA grade, operation type, education, operation time and anesthesia time, and no significant difference (P> 0.05). See table l.

Table 1: Baseline data and perioperative indicators for the three patient groups (n=20, x ± s)

group	Group D1	Group D1	Group D1
Age (age)	74.2±1.3	73.4±2.1	74.5±1.9
Gender (male / female)	15/5	14/6	16/4
Culture level (year)	6.1±1.2	6.2±0.9	6.0±1.7
Type of surgery (stomach / intestinal tumor)	9/11	10/10	8/12
ASA grade (II/III)	11/9	10/10	12/8
BMI (kg/m^2)	23.1±2.6	22.3±3.2	23.2±2.1
Time of surgery (min)	148.1±14.2	151.2±15.3	150.5±17.9
Time (min)	166.2±19.3	163.5±18.9	164.2±18.3

3. Comparing MMSE scores at different time points in the MMSE score group: all M M S E scores decreased at 1 and 3 days after surgery (P <0.01). MMSE scores at the same time point: compared with D0, D1 and D2 were higher than D0, with statistical significance (P <0.05); MMSE scores between three groups showed no statistical significance (P> 0.05); see Table 2.

Table 2: Comparison of three group MMSE scores at different time points n=20, (x ± s, points)

group	Preoperative	postoperative		
		One day, 3 days, and 7 days		
Group D1	27.9±0.9	25.9±0.7$^{\alpha\beta}$	26.3±0.5$^{\beta}$	27.1±0.7
D2 group	27.6±0.7	26.8±0.7$^{\alpha\beta}$	27.7±0.8$^{\beta}$	27.8±0.8
D0 group	27.8±0.8	23.5±0.6$^{\alpha}$	24.7±0.8	26.5±0.6
Note: Compared with the preoperative procedures,$^{\alpha}$P <0.01; when compared with the D0 group,$^{\beta}$P < 0.01				

4. Compared with the incidence of PND, PND was lower in D1 and D0 at 1 and 3 days after D2, and it was statistically significant (P <0.05). See Table 3

Table 3: Comparison of the incidence of postoperative neurocognitive impairment in the three patient groups (n=20,%)

group	The incidence of neurocognitive dysfunction is (%)		
	One day thereafter, three days thereafter, and seven days after surgery		
Group D1	1(5%)	1(5%)	0(0%)
D2 group	1(5%)	0(0%)	0(0%)
D0 group	7(35%) α	6(30%)α	2(10%)
Note: Comparison with groups D1 and D2,αP < 0.05			

5. Comparison of inflammatory response indexes at different times between TNF-and CRP: TNF-and CRP were increased on day 1 and day 3, but D1 and D2 were lower than D0, statistically significant (P <0.05), T N F in D1 and D2 and CRP decreased to basal, and D0 was also significantly reduced but still higher than D1 and D2 (P> 0.05). See Table 4.

Table 4: Comparison of inflammatory response measures for three groups at different times n=20, (x ± s)

metric	group	Preoperative	One day after surgery	Three days after surgery	Seven days after surgery
TNF-α (pg/mL)	Group D1	16.5±1.2	21.3±2.2αβ	20.5±2.3αβ	17.1±1.1
	D 2 group	16.4±1.3	20.6±3.5αβ	21.6±2.1αβ	16.7±1.3
	D 0 group	15.8±1.1	31.5±2.6α	28.2±2.9α	18.7±1.5
CRP (mg/L)	Group D1	20.4±3.5	24.5±3.7αβ	28.5±3.0αβ	20.1±3.2
	D 2 group	20.3±3.2	23.6±3.1αβ	27.6±4.1αβ	20.2±3.6
	D 0 group	19.5±3.1	27.5±3.5α	35.4±3.6α	22.5±3.1
Note: Compared with the preoperative procedures,$^{\alpha}P < 0.05$; when compared with the D0 group,$^{\beta}P < 0.01$					

6. Comparison of MAP, HR and SpO_2 at different time points of blood pressure and heart rate: MAP in D1 and D2 was significantly reduced at T 2 to T4, HR was significantly slower (P <0.05), MAP and HR in D2 at T3 and T 4, and significantly significant (P <0.05). However, SpO2 was not significant at various time points (P> 0.05). See Table 5.

Table 5: Comparison of n=20 for MAP, HR, and SpO2 (x ± s)

metric	group	T1	T2	T3	T4
MAP(mmgh)	Group D 1	84.4±6.1	82.1±6.5$^{\alpha}$	75.2±6.2$^{\alpha}$	78.2±6.5$^{\alpha}$
	D 2 group	84.1±7.6	81.4±5.3$^{\alpha}$	70.6±5.3$^{\alpha\beta}$	76.1±7.4$^{\alpha}$
	D0 group	83.7±8.1	86.4±7.6	81.1±6.7	88.4±8.2
HR (sub / sub)	Group D 1	76.3±5.1	67.3±6.5$^{\alpha}$	63.2±7.6$^{\alpha}$	66.7±7.1$^{\alpha}$
	D 2 group	75.4±6.2	62.2±7.6$^{\alpha\beta}$	58.4±6.2$^{\alpha\beta}$	61.3±6.6$^{\alpha}$
	D0 group	77.1±4.4	79.3±7.1	73.3±7.1	78.2±7.3
Spo2(%)	Group D 1	98.1±1.3	97.5±1.3	98.1±1.2	98.2±1.1
	D 2 group	98.5±1.2	98.1±1.4	97.1±1.4	97.1±1.6
	D0 group	98.2±1.1	98.2±1.0	98.2±1.1	98.2±1.3
Note: Comparison with Group D0,$^{\alpha}P < 0.05$; when compared with group D1,$^{\beta}P < 0.05$					

7. Other intraoperative anesthetic consumption, use of vasoactive drugs and postoperative recovery: D1, D2 respiratory function recovery time (min), tube dialing time (min), min) (m i n) were significantly shortened compared with D0, the intraoperative propofol use was significantly reduced, and the difference was statistically significant (P <0.05). Vasascular active drug use was reduced in the D0 group and D1 group compared with the D2 group. See Table 6.

Table 6: Inoperative anesthetic consumption, vasoactive drug use, and postoperative recovery n=20, (x ± s)

metric	D1	D2	D0
propofol (mg)	507.5±98.7$^{\alpha}$	497.5±106.2$^{\alpha}$	678.5±105.5
Respiratory recovery time (min)	10.3±2.8$^{\alpha}$	11.6±2.2$^{\alpha}$	14.3±2.1
Extubation time (min)	14.7±3.8$^{\alpha}$	15.8±3.1$^{\alpha}$	18.2±4.1
Restore Force Time (min)	20.3±4.2$^{\alpha}$	21.1±3.8$^{\alpha}$	25.3±5.7
atropine [Example (%)]	2(10)	9(45)β	1(5)
For ephedrine [Example (%)]	3(15)	8(40)β	1(5)
Note: Comparison with Group D0,$^{\alpha}P < 0.05$; when compared with groups D0 and D1, $^{\beta}P < 0.05$			

Discuss

Intravenous anesthetic drugs have multiple effects on brain physiology, and they are dose-related changes. Studies have shown that propofol infusion to volunteers disappeared from consciousness, and brain glucose metabolism was measured by positron emission tomography (PET), and found that the whole brain metabolic rate decreased by 48% to 58%, and the decrease in brain metabolic rate caused a decrease in energy consumption. The brain consumes energy to maintain the ion gradient inside and outside the cell, which can reflect the change in depolarization and repolarization electrical activity occurring on the EEG (EEG), which may cause the explosive inhibition of the EEG. Enropy index monitoring is a non-linear analysis of EEG, compared with the EEG double-frequency index (BIS) monitoring, entropy index module including reaction entropy (RE) and state entropy (SE), SE mainly reflects the functional condition of cerebral cortex, RE mainly reflects the subcortical inhibition and frontal myelectric excitation, entropy index RE is a fast response index, can not only monitor the degree of analgesia, and BIS can only monitor sedation. Current animal experiments show that excessive anesthetics can cause neuropathological changes, namely, increasing A in the animal brainβSediment and Tau aggregation, whether the potential neurotoxic effects of anesthetics are similar to Alzheimer's disease (AD), that is, anesthetics can cause altered neurocognitive function such as AD, leading to postoperative neurocognitive impairment (PND) [5, 6]. Based on the correlation between the entropy index and the effect of the anesthetic drugs, this study used RE as the target index of the intraoperative anesthesia depth, with RE values set at 40 to 60 and SE set to 30~50 to guide the intraoperative anesthetic medication. In this study, the amount of propofol used for DM combined with DM (D1) and DM (D2) were (507.5 ± 98.7) mg and (497.5 ± 106.2) mg, respectively, Compared with the control group (the D0 group) (678.5 ± 105.5), mg propofol decreased by 25.2% and 26.6%, respectively; Shufentanyl fell by 29.2% and 30.3%, respectively; At the same time, breathing recovery time, extubation time and directional force recovery time are significantly shortened, The difference was statistical significant (P <0.05), It shows that monitoring the entropy index is obviously helpful to reduce anesthetic drug exposure, maintain appropriate anesthesia level and improve cognitive function in surgical patients [7].

The MMSE scale is simple and time-consuming and is one of the most widely used cognitive screening scales. In this study, the MMSE scores were decreased at 1 and 3 days compared with those before surgery, but groups D1 and D2 were higher than D0 (P <0.01), and the incidence of PND in groups 1 and 3 days after D1 was lower than D0 (P <0.05).Show that cognitive function will be affected in a short time after surgery, and by monitoring the entropy index, can accurately monitor EEG timely guide control of general anesthesia depth, accurately determine patient consciousness, can quickly detect anesthesia depth and strong pain stimulation response, in order to adjust the anesthetic, reduce central neuron drug exposure time, reduce neurotoxicity and inflammatory response, improve postoperative cognitive function in elderly patients [8-10]. Ballard C It is also believed that too deep anesthesia is often accompanied by the overdose of anesthetic drugs, and the intraoperative monitoring of anesthesia depth is recommended to reduce the incidence of PND [11].

This study of chest elective surgery 60 elderly patients as research object, into the standard: patients between 65 and 88 years old, three average age of 74.6 years old, is the most obvious stage of anesthesia and surgical tolerance decline, anesthesia management easily cause central, circulation, respiratory function, they are highly susceptible to PND. In the prevention of PND can to change the surgical mode and age, it is particularly necessary to strengthen intraoperative drug intervention. In recent years, clinical studies at home and abroad have shown that dexmetomidine has central anti-sympathetic, anti-inflammatory response, anti-injury signaling, and can increase the concentration of acetylcholine, improve orientation, memory, maintain cognitive function, and has sedative and analgesic effects [12-15]. Yang Duo et al [16]. The study found that in addition to analgesia and sympathetic inhibition, dexmetomidine also has significant sedative and anxiolytic effects, producing sedation effects similar to natural sleep, and significantly decreased anesthesia trend index (Narcotrend index, NI) compared with the control group.

The authors found above 0.6 g • kg-1•h-1Induction, can reduce the reaction entropy by about 40% on average, theoretically can enhance the anesthetic effect, using the entropy index to drip the DEX can be targeted for intraoperative management, reduce the blindness of anesthetic drug infusion. Wang Jingjun other studies reported that the anxiolytic and sedation effects obtained with different doses of DEX were ideal [17]. The comparison of hemodynamic indicators showed that the blood pressure and heart rate increased in patients with OPCAB when given with DEX0.2ug/kg, and the heart rate was excessively slow at the 0.8 g / kg dose, while 0.5 / kg was the best effect. And compared with the low dose group, the incidence of PND decreased significantly at 1 and 3 days (P <0.05), and the difference was not significant at 6 days after surgery. The comparison was not significantly significant (P> 0.05).0.3 g in groups D1 and D2 • kg-1•h-1 0.6μg•kg-1•h-1Maintain the pump injection induction; The results show that, when compared to the control group, The MAP was significantly reduced at T 2 to T 4 in groups D1 and D2, HR slowed significantly, Among them, the reduction in the D2 group was particularly significant, The use of vasoactive drugs was also significantly increased, The difference was statistical significant (P <0.05), Although the TNF-and CRP were all increased on day 1 and day 3 compared with the 1 day before surgery, However, groups D1 and D2 were lower than groups D0, The difference was statistical significant (P <0.05); In comparison with the preoperative, The MMSE scores decreased in all three groups at 1 and 3 days after surgery, However, in groups D1 and D2, they were higher than in groups D0, The difference was statistical significant (P <0.01).Description tomidine 0.3 g • kg-1•h-1The use of maintenance pump injection was better in elderly patients. With the increase of dose, bradycardia and hypotension increased, reduced brain perfusion pressure, and affected the balance of supply and demand of brain oxygen, which was similar to the research effect of Wang Dongxin's team [18, 19].

In conclusion, this group showed that entropy index targeted monitoring and maintenance during dexmetomidine (DEX) cooperate on brain protection, with DEX0.3 g•kg-1•h-1Maintaining pump infusion works better in preventing perioperative neurocognitive impairment in older patients. The reason may be that dexmetomidine exerts an anti-inflammatory effect, reduces brain damage and maintains cognitive function by inhibiting the release of inflammatory mediators and neuroendocrine hormones. This study is a single-center and small-sample study, and the follow-up time is not long enough, and the long-term impact of cognitive dysfunction cannot be ignored. In the future, the brain protection mechanism of dexmetomidine should be further clarified to extend the follow-up time, and a large-sample multicenter clinical study is needed to reduce the incidence of PND.

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