Int J Clin Exp Med 2015;8(4):5649-5657
www.ijcem.com /ISSN:1940-5901/IJCEM0006273

Original Article

Effect of neoadjuvant chemotherapy on sevoflurane MAC-BAR value of patients undergoing radical stomach carcinoma surgery

Wei Du*, Chao Li*, Hemei Wang, Aihua Zhao, Junmei Shen, Fangfang Yong, Huiqun Jia

*Department of Anesthesiology, Section II, The Fourth Hospital of Hebei Medical University, No. 12, Jiankang Road, Shijiazhuang 050011, Hebei Province, China. *Equal contributors.*

Received January 23, 2015; Accepted March 20, 2015; Epub April 15, 2015; Published April 30, 2015

Abstract: Objective: To determine the minimum alveolar concentration (MAC) of sevoflurane required for 50% blockade of the adrenergic response (BAR) to surgical incision in patients treated with neoadjuvant chemotherapy prior to radical gastrectomy. Patients and design: Forty-four patients were selected for this study. Patients with preoperative neoadjuvant chemotherapy comprised the NC group (n = 22) and patients without preoperative neoadjuvant chemotherapy were included as the C group (n = 22). Patients in the NC group were treated with two cycles of 14-day neoadjuvant chemotherapy with combination of oxaliplatin and Gio, and underwent surgery 3 weeks later. Patients in the C group received no chemotherapy prior to surgery. A sequential allocation method was employed to determine the MAC-BAR for each group. The initial end-tidal concentration of sevoflurane was set as 3% for both the NC and C groups. Sympathetic responses to surgical incision were evaluated 6 times by measuring the heart rate (HR) and mean arterial blood pressure (MAP) at 1 min intervals before (T1, T2, T3) and after (T4, T5, T6) skin incision, and used to adjust the end-tidal sevoflurane concentrations for each patient. More than a 15% increase in MAP or HR after incision was scored as a positive response. Main results: The HR and MAP levels measured pre- (T1) and post-incision (T6) were significantly lower than base line values at admission in both groups, but without statistical difference between the groups. The MAC-BAR value of sevoflurane was 2.2% in the NC group and 3.0% in the C group ($P < 0.05$). Conclusions: Neoadjuvant chemotherapy reduced the MAC-BAR value of sevoflurane in gastric cancer patients by enhancing the inhibitory effect of sevoflurane on the stress response.

Keywords: Antineoplastic chemotherapy regimens, anesthetic, inhalation, dose-response relationships, drugs, stress

Introduction

Stomach cancer is common in China and its incidence rate ranks among the top three of malignant tumors [1]. Unfortunately, the majority of gastric cancers are diagnosed at an advanced state, which influences the overall therapeutic outcome of the treatment. A therapeutic surgical approach, known as neoadjuvant chemotherapy, was reported in 1982 [2] and became a research focus in the field of locally advanced gastric cancer treatments. Subsequently, the comprehensive treatment of gastric cancer received widespread attention [3-5].

Neoadjuvant chemotherapy (NC) is a systemic chemotherapy employed for the treatment of cancer patients. In contrast to adjuvant chemotherapy, it is the first step in treatment prior to topical therapies such as local surgery or radiotherapy. NC has been reported to reverse various stages of tumor growth and reduce the extent of surgery required, as well as to improve significantly the overall survival rate of patients [3-5].

As the depth of anesthesia is an important factor affecting postoperative complications and survival, an understanding of the effects of chemotherapeutic drugs on anesthesia will enable doctors to administer efficient anesthesia to patients undergoing surgery [6, 7]. Chemotherapy with platinum-based agents is known to be associated with neurotoxicity. For exam-

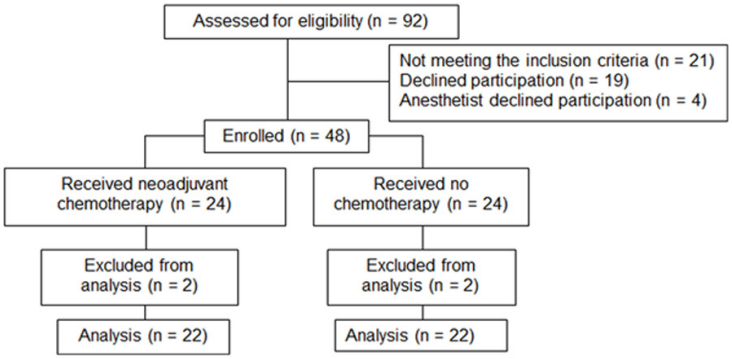

Figure 1. Flow chart of patients who participated in the clinical trial. NC patients received preoperative neoadjuvant chemotherapies and C patients were operated without chemotherapies.

ple, oxaliplatin, a third-generation platinum-based drug with low toxicity, causes primarily sensory nerve lesions, such as paresthesia and numbness of the extremities and can produce both acute and chronic neurotoxicity [8]. Symptoms of acute neurotoxicity appear within a few hours after treatment and peak at 24~48 h and last for 7 days. The symptoms include impairments in the performance of the lower extremities and perioral sensory impairments such as paresthesia, with mouth and throat muscle tension. Oxaliplatin exerts its acute toxicity by delaying inactivation of the voltage-gated Na^+ channel located on the membrane of the myelinated afferent nerve cell, which results in an increase in Na^+ influx that produces the acute neurological symptoms [9]. Chronic treatment with oxaliplatin has been shown to affect the dorsal root ganglia (DRG), causing an axonal neuropathy [8]. 5-fluorouracil (5-FU), in concentrations that are clinically relevant, has toxic effects on progenitor cells and oligodendrocytes of the central nervous system. Systemic administration of 5-FU causes acute CNS injuries, which leads to a syndrome involving progressive but delayed deterioration of oligodendrocytes and myelinated nerve fibers (myelin lesions) [10]. Also, in animal experiments functional changes in specific brain regions, including the frontal lobes and hippocampus, have been reported after methotrexate and 5-FU applications [11]. Tagafur, a derivative of the oral anticancer agent 5-FU, is a major component of combination chemotherapy used to treat advanced gastric cancer. It is metabolized in the body to 5-FU. The other components of combination therapy are oteracil and jigme pyrimidine, which regulate 5-FU production thereby reducing the toxic side effects. Sevoflurane is an inhalational general anesthetic and is widely used because of its rapid rate of onset and offset, better hemodynamic stability, and limited irritation actions of mucous membranes. The mechanism of anesthetic action of sevoflurane remains unknown but may involve direct or indirect actions at nicotinic acetylcholine, glycine, γ-aminobutyric acid (GABA) and glutamate receptors [12-14].

Neoadjuvant chemotherapy involves anticancer drugs with neurotoxicity, which as mentioned above, pathologically affects the nervous systems; therefore the sevoflurane sensitivity of patients treated with neoadjuvant chemotherapy might be altered [9, 15-17].

In the present study, we determined the minimum alveolar concentration of sevoflurane, which blocks 50% of the adrenergic response to surgical incision (MAC-BAR) in patients treated with neoadjuvant chemotherapy. We anticipated that understanding the effect of neoadjuvant chemotherapy on the potency of sevoflurane might help us develop a more effective and safer anesthesia regimen.

Materials and methods

Baseline data of patients and neoadjuvant chemotherapy

This study was approved by the hospital medical ethics committee and authenticated with informed consent forms signed by patients or their families. Initially, 92 patients were assessed for eligibility but 21 did not meet the inclusion criteria, while 19 declined to participate and the anesthetist excluded 4. Of the 48 enrolled patients, 44 were finally included in the statistical evaluation, because 4 were excluded for analysis after the interventions (**Figure 1**). Forty-eight patients underwent radical operation for carcinoma of the stomach from December 2011 to January 2013. These patients were 40 to 64 years old with body-mass indexes (BMIs) of 18~30 kg/m^2 and American Society of Anesthesiologists (ASA)

physical state grading of I or II, no history of hypertension, and were not on drugs that could affect the circulatory system or sympathetic drugs prior to operation. Patients were divided into two groups, a neoadjuvant chemotherapy group (NC group, *n* = 22) and a control group (C group, *n* = 22). Patients in the NC group received preoperative chemotherapy for 2 cycles of 14-day treatment with a combination of oxaliplatin 150 mg/qd and Gio 60 mg/bid, and received surgery 3 weeks after the commencement of chemotherapy. Patients in the C group underwent surgery without neoadjuvant chemotherapy. Patients who fell into the following criteria were excluded from the study. Exclusion criteria: 1) patients having diseases of the cardiovascular system, respiratory system, liver or kidneys; 2) patients with a history of mental or neurological disease; 3) patients having an acid-base and electrolyte imbalance, diabetes or endotoxemia; 4) patients treated with drugs which might affect the MAC-BAR measurement, such as the preoperative sedatives midazolam and nonsteroidal anti-inflammatory drugs (NSAIDs), as well as patients with a history of alcoholism or drug abuse; 5) patients with a mean arterial pressure (MAP) < 50 mmHg or a HR < 50 beats/min before incision.

Anesthesia and MAC-BAR determination

Prior to surgery, patients were not administered any drugs that might affect the circulatory or sympathetic nervous systems. Fasting time for food was 8 h and for water 6 h preoperatively. Patients were infused with sodium chloride by injection via the peripheral venous route at a rate of 10 mL/kg/h. Electrocardiography (ECG), oxygen saturation (SpO_2) and bispectral index (BIS) (EEG monitor AspectA-2000, BIS Monitor, USA) were monitored and radial artery catheterization performed under local anesthesia as an invasive method to measure arterial blood pressure. Anesthesia was induced by target-controlled infusion of propofol (AstraZeneca, London, UK) and remifentanil (Yichang Humanwell Pharmaceutical Co., Yichang, China) to produce a plasma concentration of 3 μg/mL and 4 ng/mL, respectively. This controlled anesthesia method was used because sufficient depth of anesthesia can be quickly achieved after intravenous infusion of these drugs, the target plasma concentration equilibrium is reached rapidly and the context-sensitive half-time ($t_{½}$cs) is very short; $t_{½}$cs of propofol is 4 min [18] and remifentanil 3~5 min [19]. After patients lost consciousness, 0.6 mg/kg rocuronium (NV Organon, Oss, Netherlands) was intravenously injected and endotracheal intubation and mechanical ventilation was carried out. The tidal volume was set as 8 mL/kg, the inspiratory to expiratory ratio 1:1.5. The breathing frequency was regulated to maintain a partial pressure of end-tidal carbon dioxide ($PETCO_2$) 35-45 mmHg (1 mmHg = 0.133 kPa). Immediately after stopping intravenous infusion of propofol and remifentanil, patients began to inhale sevoflurane. The target plasma concentrations of propofol and remifentanil decreased to a significantly low level and after 20 min reached 0.2 μg/ml and 0.1 ng/ml, respectively. These levels are consistent with their pharmacokinetic properties, suggesting that these drugs had no significant clinical effect in determining the sevoflurane MAC-BAR. The end tidal concentration of sevoflurane (Gas Density DetectorSmart Anesthesia Multi-gas Module/NO O_2 Sensor (GE Co. Wuxi, China) quickly reached the target value and lasted 15 min.

A sequential allocation method was employed to adjust the end-tidal sevoflurane concentration for patients. The initial concentration for the first patient in both groups was 3%. According to the patient's sympathetic response to the incision, the sevoflurane concentration was adjusted as appropriate for the next patient. When a patient responded or did not respond to the incision, a 1.2 times higher or lower concentration of the drug was used for the next patient. More than 6 wave-patterns of negative/positive responses (crossovers) were obtained. When the pre-incision MAP value was less than 50 mmHg, 6 mg of ephedrine was intravenously administered and when the HR was less than 50 beats/min, 0.5 mg atropine was administered, and the patient was excluded from the study. As a result, the next patient received sevoflurane at the end-tidal concentration assigned for the previously excluded patient. The HR and the MAP values were recorded at 2 min (T1), 1 min (T2) and immediately (T3) prior to skin incision, and immediately (T4), 1 min (T5) and 2 min (T6) after incision. The average values of HR and MAP before and after incision were calculated. When the ampli-

Table 1. Comparison of baseline data between patients allocated to the control (C) group and the neoadjuvant chemotherapy (NC) group (*n = 22, $\bar{x}$ ± SD)*

	C group	NC group
Age (years)	51 ± 5	53 ± 4
Gender (F/M)	9/13	7/15
Course of Disease (years)	5.2 ± 1.9	5.7 ± 1.5
BMI (kg/m^2)	25.1 ± 2.7	24.2 ± 1.9
HR (beat/min)	77 ± 6	76 ± 6
MAP (mmHg)	90 ± 5	87 ± 4
BIS	95.1 ± 0.9	93.9 ± 0.8
Hb (mg/mL)	126 ± 9	119 ± 8
Alb (mg/mL)	35.1 ± 1.2	35.2 ± 0.8
Cancer Staging (stage)	IIB~IIIC	IIB~IIIC

BMI: body mass index, HR: heart rate, MAP: mean arterial blood pressure, BIS: bispectral index, Hb: hemoglobin, Alb: albumin.

tude of variation of the HR or the MAP values after the incision was less than 15% it was scored as positive, signifying that the patient's sympathetic response to the incision was not inhibited by sevoflurane at the administered end-tidal concentration.

The occurrence of intraoperative awareness and the 1st-day postoperative condition of the patients were monitored and recorded. The sevoflurane MAC-BAR values were calculated according to the sequence and the number of turning point methods [20].

Statistical analyses

Values from two groups are presented as mean ± SD. Statistical analyses were performed using the SPSS13.0 version for Windows (Chicago, SPSS Inc.). All original data were first analyzed with Shapiro-Wilk test to examine whether data were in normal distribution or not. Student t test was used to compare data with normal distribution and with homogeneity of variance; Welch's correction t test was used for data with heterogeneity of variance. Mann-Whitney U test was used for data in non-normal distribution. $P < 0.05$ was considered statistically significant.

Results

Among the 48 patients in the study, 2 each in the NC group and in the C group had a MAP value of < 50 mmHg or a HR value of < 50 beats/min before skin incision. They were therefor administered vascular active drugs and excluded from the study.

The remaining 44 patients were divided equally into two groups, 22 patients in the C group and 22 patients in the NC group. The patients' base line data were compared between the two groups. In terms of average age, gender, BMI, course of the disease, and the stage of cancer, there were no obvious differences between the groups (**Table 1**). Physiological indices such as HR, MAP, BIS prior to anesthesia, and the levels of hemoglobin (Hb) and albumin (Alb) were not statistically significantly different ($P > 0.05$) (**Table 1**). The HR and the MAP values measured in pre- (T1) and post-incision (T6) were significantly lower than the values at admission T (0) in both groups. The 2 min post-incision (T6) values were significant higher than the 2 min pre-incision (T1) values. However, there was no statistically significant difference between the groups (**Table 2**). No intraoperative awareness of the patients was observed in either group.

Determination of the end-tidal sevoflurane concentration by the sequential allocation method using patients' response to skin incision generated two distinctively different wave-patterns in the C and NC groups (**Figures 2** and **3**). The sevoflurane MAC-BAR value and its 95% confidence interval (96% CI) were calculated based on these data. The sevoflurane MAC-BAR value in the C group was 3.0% (95% CI, 2.7-3.2%) and in the NC group 2.2% (95% CI, 2.0-2.4%), respectively, demonstrating statistically significant difference between the two groups ($P < 0.0001$) (**Table 3**).

Discussion

The MAC value of healthy adults for sevoflurane was reported to be 1.71% [21], and the MAC-BAR value was 2.56%, 1.5 times higher than the MAC [22]. The preliminary experiments showed that an excessively high concentration of expiratory sevoflurane caused a significant decrease in HR and MAP values, which might greatly increase the risk of accidental cardiovascular damage in patients. According to published data, the equilibrium time of sevoflurane was longer than 15 min [23, 24]. Although the target tidal concentration of sevoflurane can be

Table 2. Changes in mean arterial blood pressure (MAP) and heart rate (HR) of patients in control (C) and in neoadjuvant chemotherapy (NC) group before and after skin incision (*n = 22* per each group)

TIME before or after skin incision	MAP (mmHg)				HR (bpm)			
	C	*P*	NC	*P*	C	*P*	NC	*P*
T0 (at admission)	90 ± 5		87 ± 4		77 ± 6		76 ± 6	
T1 (2 min pre-incision)	61 ± 6	< 0.0001^{*,a}	62 ± 4	< 0.0001^{*,a}	64±10	< 0.0001^{*,a}	62 ± 5	0.0029^{*,c}
T2 (1 min pre-incision)	62 ± 8		62 ± 4		64 ± 10		61 ± 5	
T3 (immediately before)	62 ± 8		62 ± 4		64 ± 10		61 ± 5	
T4 (immediately after)	64 ± 9		63 ± 5		66 ± 11		63 ± 5	
T5 (1 min post-incision)	73 ± 9		72 ± 7		72 ± 9		72 ± 8	
T6 (2 min post-incision)	76 ± 11	0.0003^{*,b} < 0.0001$^{\Delta,b}$	77 ± 11	< 0.0001^{*,c} 0.0003$^{\Delta,c}$	75 ± 11	0.0504^{*,c} 0.0029$^{\Delta,c}$	75 ± 12	0.0504^{*,c} 0.0029$^{\Delta,c}$

*: Compared with T0; $^{\Delta}$: compared with T1. ^{a}: indicating the *P* value from t test; ^{b}: indicating the *P* value from Welch's correction t test; ^{c}: indicating the *P* value from Mann Whitney U test.

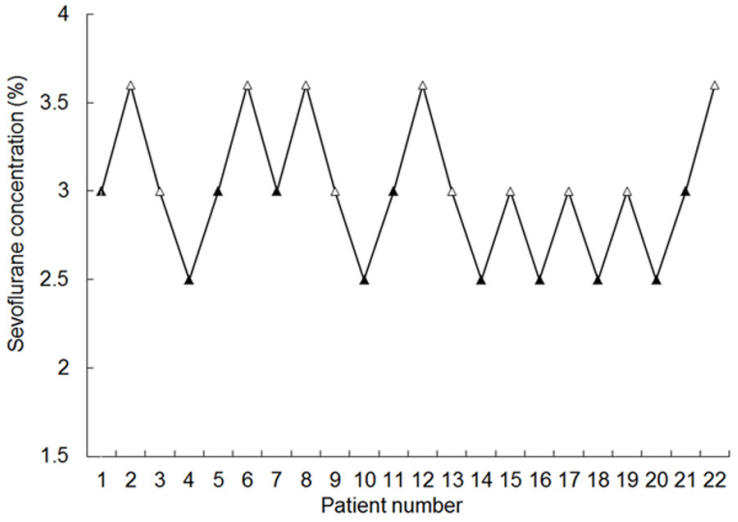

Figure 2. Individual responses to skin incision obtained by the sequential allocation method in patients who received no neoadjuvant chemotherapy prior to surgery (C group). When a patient showed an increase in either HR or MAP of 15% or more from the pre-incision value, the end-tidal concentration of sevoflurane given to the next patient was increased (positive response [*solid triangles*]), whereas in the absence of an increase in either HR or MAP of 15% or more from the pre-incision value, the end-tidal concentration given to the next patient was decreased (negative response [*open triangles*]).

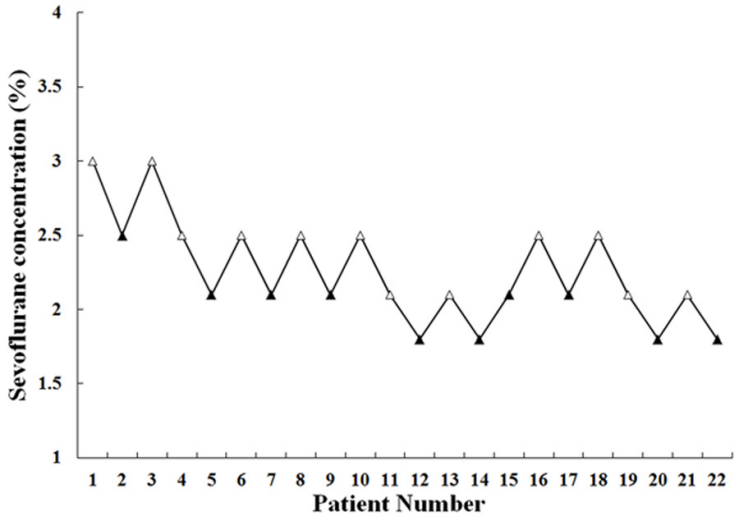

Figure 3. Individual responses to skin incision obtained by the sequential allocation method in patients who received neoadjuvant chemotherapy prior to surgery (NC group). When a patient showed an increase in either HR or MAP of 15% or more from the pre-incision value, the end-tidal concentration of sevoflurane given to the next patient was increased (positive response [*solid triangles*]), whereas in the absence of an increase in either HR or MAP of 15% or more, the end-tidal concentration given to the next patient was decreased (negative response [*open triangles*]).

achieved within 15 min, a longer equilibration time should be used for the determination of the MAC value to ensure that the alveolar gas and its partial pressure in the brain reach dynamic equilibrium under constant alveolar ventilation. Therefore, despite the MAC value for sevoflurane being reported as 1.71% [21], we set the initial end-tidal sevoflurane concentration for this study at 3%, which allowed the equilibrium time to be 15 min and the partial pressure of anesthetic gas in arterial blood, lung and the brain to reach dynamic equilibrium.

To determine MAC-BAR, we used the sequential allocation method utilizing a patient's sympathetic response to surgical skin incision. The positive response was defined by a fold increase in HR or MAP values as compared to those measured before skin incision, as previously reported [23, 24]. Our sequential allocation experiment generated more than 6 wave-patterns of negative/positive reactions (crossovers). The number of crossovers is an important factor for MAC estimates. Dixon stated four crossovers were sufficient to estimate MAC [25], however Paul *et al.* reported that more than six crossovers greatly increased the authenticity of the MAC estimation [20].

We have shown that the MAC-BAR value of sevoflurane in the NC group was significantly lower than that in the C group, indicating that neoadjuvant chemotherapy reduced the gastric sevoflurane MAC-BAR value of patients. He *et al.* observed that neoadjuvant chemotherapy lowered the 50% effective dose (ED_{50}) of intravenous anesthetics [26], such as propofol and etomidate in patients. The reason for this might be that neoadjuvant chemotherapy causes liver damage resulting in abnormal lipid

Table 3. Sevoflurane MAC-BAR and its 95% confidence interval (95% CI) in the control (C) and neoadjuvant chemotherapy (NC) group (n = 22 per each group)

Group	MAC-BAR (%)	95% IC (%)
C	3.0	2.8~3.2
NC	2.2[a]	2.0~2.3[a]

[a]: Comparison between the C and NC groups with Mann Whitney U test , $P < 0.0001$.

metabolism, which affects the metabolism of lipid-formulated intravenous anesthetic drugs. However, inhalation anesthetics, such as sevoflurane, are not metabolized in the liver but are discharged mainly from the lung, a small amount through the skin, and by the kidney in its original form. Increasing numbers of clinical studies have shown showed that chemotherapies with the clinically effective doses of drugs increases the risk of damaging the patients' nervous system [27, 28]. Schlegel *et al.* reported that chemotherapy drugs have toxic effects on the CNS through a variety of mechanisms and may lead to reversible or even irreversible neurological dysfunction [29]. Winocur *et al.* observed that the standard dose of 5-FU caused disability of spatial memory and learning in adult BALB/C mice [11]. This cognitive dysfunction was similar to the phenomena observed in patients treated with chemotherapeutic drugs. It is also known that standard dose chemotherapy negatively affects cognitive function and causes nervous system damage in patients with cancer. Since the targets of inhaled anesthetics are located in the CNS, the increase in the potency of sevoflurane observed for patients in the NC group may attributed to damage of the nervous system caused by the neoadjuvant chemotherapy drugs, oxaliplatin and Gio. It is likely that the damaged CNS was sensitized to inhaled anesthetics so that the effectiveness of the anesthetics was enhanced in patients receiving chemotherapy but the precise mechanisms remain to be elucidated.

In our experiment, the sevoflurane MAC-BAR value of the non-chemotherapy patients was 3.0%. Ura *et al.* measured a sevoflurane MAC-BAR value of 8.0 ± 0.2% by employing the sequential allocation method similar to ours [30]. Katoh *et al.* used sevoflurane alone and reported that the MAC-BAR value was 4.15% [24]. One of the reasons for the discrepancy in the sevoflurane MAC-BAR values might be the age range of the patients recruited in the study. The patients' ages in our study were between 40 and 64 years, while those in Ura's study ranged from 20 to 49 years. Presently, the effects of the age factor on neoadjuvant chemotherapy and on the determination of MAC-BAR value are not clear and further study is required to address this important question. Another reason for the discrepancy might be that Ura's group used more stringent criteria for the positive sympathetic response to surgical incision. They included in their criteria, an increase of more than 10% in the plasma norepinephrine concentration compared to the pre-incision level, in addition to MAP.

In summary, we have found that neoadjuvant chemotherapy enhances the inhibitory effect of sevoflurane on the sympathetic response of cancer patients undergoing radical gastrectomy, thereby reduced the sevoflurane MAC-BAR value.

Acknowledgements

We would especially like to thank Prof. Yunshui Peng, Prof. Zixian Song and Prof. Shuxian Li for many helpful discussion and technical support.

Disclosure of conflict of interest

None.

Address correspondence to: Huiqun Jia, Department of Anesthesiology, Section II, The Fourth Hospital of Hebei Medical University, No. 12, Jiankang Road, Shijiazhuang 050011, China. Tel: +86-0311-86095371; Fax: +86-0311-6077634; E-mail: jiahq140605@126.com

References

[1] de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D and Plummer M. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol 2012; 13: 607-615.

[2] Frei E 3rd. Clinical cancer research: an embattled species. Cancer 1982; 50: 1979-1992.

[3] Hirakawa M, Sato Y, Ohnuma H, Takayama T, Sagawa T, Nobuoka T, Harada K, Miyamoto H, Sato Y, Takahashi Y, Katsuki S, Hirayama M, Takahashi M, Ono M, Maeda M, Takada K, Hayashi T, Sato T, Miyanishi K, Takimoto R,

Kobune M, Hirata K and Kato J. A phase II study of neoadjuvant combination chemotherapy with docetaxel, cisplatin, and S-1 for locally advanced resectable gastric cancer: nucleotide excision repair (NER) as potential chemoresistance marker. Cancer Chemother Pharmacol 2013; 71: 789-797.

[4] Inoue K, Nakane Y, Kogire M, Fujitani K, Kimura Y, Imamura H, Tamura S, Okano S, Kwon AH, Kurokawa Y, Shimokawa T, Takiuchi H, Tsujinaka T and Furukawa H. Phase II trial of preoperative S-1 plus cisplatin followed by surgery for initially unresectable locally advanced gastric cancer. Eur J Surg Oncol 2012; 38: 143-149.

[5] Xu AM, Huang L, Liu W, Gao S, Han WX and Wei ZJ. Neoadjuvant chemotherapy followed by surgery versus surgery alone for gastric carcinoma: systematic review and meta-analysis of randomized controlled trials. PLoS One 2014; 9: e86941.

[6] Monk TG, Saini V, Weldon BC and Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg 2005; 100: 4-10.

[7] Leslie K, Myles PS, Forbes A and Chan MT. The effect of bispectral index monitoring on long-term survival in the B-aware trial. Anesth Analg 2010; 110: 816-822.

[8] Lehky TJ, Leonard GD, Wilson RH, Grem JL and Floeter MK. Oxaliplatin-induced neurotoxicity: acute hyperexcitability and chronic neuropathy. Muscle Nerve 2004; 29: 387-392.

[9] Adelsberger H, Quasthoff S, Grosskreutz J, Lepier A, Eckel F and Lersch C. The chemotherapeutic oxaliplatin alters voltage-gated Na (+) channel kinetics on rat sensory neurons. Eur J Pharmacol 2000; 406: 25-32.

[10] Han R, Yang YM, Dietrich J, Luebke A, Mayer-Proschel M and Noble M. Systemic 5-fluorouracil treatment causes a syndrome of delayed myelin destruction in the central nervous system. J Biol 2008; 7: 12.

[11] Winocur G, Vardy J, Binns MA, Kerr L and Tannock I. The effects of the anti-cancer drugs, methotrexate and 5-fluorouracil, on cognitive function in mice. Pharmacol Biochem Behav 2006; 85: 66-75.

[12] Garcia PS, Kolesky SE and Jenkins A. General anesthetic actions on GABA (A) receptors. Curr Neuropharmacol 2010; 8: 2-9.

[13] Scheller M, Bufler J, Schneck H, Kochs E and Franke C. Isoflurane and sevoflurane interact with the nicotinic acetylcholine receptor channels in micromolar concentrations. Anesthesiology 1997; 86: 118-127.

[14] Stucke AG, Stuth EA, Tonkovic-Capin V, Tonkovic-Capin M, Hopp FA, Kampine JP and Zuperku EJ. Effects of sevoflurane on excitatory neurotransmission to medullary expiratory neurons and on phrenic nerve activity in a decerebrate dog model. Anesthesiology 2001; 95: 485-491.

[15] Diao S, Ni J, Shi X, Liu P and Xia W. Mechanisms of action of general anesthetics. Front Biosci (Landmark Ed) 2014; 19: 747-757.

[16] Petrenko AB, Yamakura T, Sakimura K and Baba H. Defining the role of NMDA receptors in anesthesia: are we there yet? Eur J Pharmacol 2014; 723: 29-37.

[17] Uhrig L, Dehaene S and Jarraya B. Cerebral mechanisms of general anesthesia. Ann Fr Anesth Reanim 2014; 33: 72-82.

[18] Shafer A, Doze VA, Shafer SL and White PF. Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. Anesthesiology 1988; 69: 348-356.

[19] Westmoreland CL, Hoke JF, Sebel PS, Hug CC Jr and Muir KT. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. Anesthesiology 1993; 79: 893-903.

[20] Paul M and Fisher DM. Are estimates of MAC reliable? Anesthesiology 2001; 95: 1362-1370.

[21] Katoh T and Ikeda K. The minimum alveolar concentration (MAC) of sevoflurane in humans. Anesthesiology 1987; 66: 301-303.

[22] Roizen MF, Horrigan RW and Frazer BM. Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision--MAC BAR. Anesthesiology 1981; 54: 390-398.

[23] Albertin A, Casati A, Bergonzi P, Fano G and Torri G. Effects of two target-controlled concentrations (1 and 3 ng/ml) of remifentanil on MAC(BAR) of sevoflurane. Anesthesiology 2004; 100: 255-259.

[24] Katoh T, Kobayashi S, Suzuki A, Iwamoto T, Bito H and Ikeda K. The effect of fentanyl on sevoflurane requirements for somatic and sympathetic responses to surgical incision. Anesthesiology 1999; 90: 398-405.

[25] Dixon WJ. Staircase bioassay: the up-and-down method. Neurosci Biobehav Rev 1991; 15: 47-50.

[26] He ZJ, Hu YH and Fan ZY. Median effective effect-site concentration of intravenous anesthetics for loss of consciousness in neoadjuvant chemotherapy patients. Chin Med J (Engl) 2011; 124: 504-508.

[27] Newton HB. Neurological complications of chemotherapy to the central nervous system. Handb Clin Neurol 2012; 105: 903-916.

[28] Sioka C and Kyritsis AP. Central and peripheral nervous system toxicity of common chemothe-

rapeutic agents. Cancer Chemother Pharmacol 2009; 63: 761-767.

[29] Schlegel U. Central nervous system toxicity of chemotherapy. European Association of NeuroOncology Magazine 2011; 1: 25-29.

[30] Ura T, Higuchi H, Taoda M and Sato T. Minimum alveolar concentration of sevoflurane that blocks the adrenergic response to surgical incision in women: MACBAR. Eur J Anaesthesiol 1999; 16: 176-181.