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Analgesic effect of the midazolam-induced anesthesia in different doses on the patients after the thoracoscopic resection of lung cancer

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ABSTRACT

Objective: To elaborate the analgesic efficiency of midazolam-induced anesthesia in different doses on the patients following the thoracoscopic resection of lung cancer.
Methods: Ninety patients undergoing thoracoscopic resection of lung cancer between August 2017 and July 2018 were randomized in the observation group (n = 45) and the control group (n = 45). Patients in observation group underwent the anesthesia induced by 0.1 mg/kg midazolam, while for the control group, the dose was adjusted to 0.05 mg/kg. Then, we compared the levels of inflammatory factors, SaO_2, average of arterial pressure and changes in heart rate before and after surgery (48 h) to analyze the efficacy.
Results: At the postoperative 48 h, patients in the observation group had lower levels of inflammatory factors when comparing with their counterparts in the control group [IL-6, IL-8, IL-1β and TNF-α: (58.44 ± 3.22) μg/L, (2.04 ± 0.26) μg/L, (2.98 ± 0.44) μg/L, (5.33 ± 0.77) μg/L *v.s.* (96.44 ± 4.54) μg/L, (3.23 ± 0.33) μg/L, (3.77 ± 0.44) μg/L, (7.64 ± 0.99) μg/L] ($P < 0.05$). Meanwhile, those in the observation group had a lower SaO_2, average arterial pressure and heart rate [(93.79 ± 1.08)%, (93.22 ± 3.46) mmHg, (87.55 ± 2.35) beat/min *v.s.* (97.13 ± 1.03)%, (96.44 ± 4.03) mmHg, (91.05 ± 2.89) beat/min] ($P < 0.05$). However, no statistical significance was identified in the differences of the bleeding amount, surgical time and anesthesia time between two groups ($P > 0.05$), while the eye-opening time and the extubation time in the observation group were all shorter than those in the control group ($P < 0.05$). Similarly, the postoperative pain scores, total doses of propofol and remifentanil were also lowered ($P < 0.05$).
Conclusion: For patients of thoracoscopic resection of lung cancer, midazolam-induced anesthesia (0.1 mg/kg) performs better than 0.5 mg/kg in inhibiting the inflammatory responses, with significant reduction in the dose of anesthetics, thereby stabilizing the status of patients in perioperative period and mitigating the postoperative pains. Thus, it is potential candidate.

Lung cancer is characterized as a tumor with a high prevalence and mortality rate, and men have a high incidence rate than females (Gao et al., 2017a,b,c; Rashid and Takabe, 2012).

Smoking is a major pathogen for lung cancer, and the prevalence of lung cancer in population with smoking habit is 10–20 times that of the normal population, which is even higher in the younger population (Gao et al., 2017a,b,c; McKenna et al., 2006; Villamizar et al., 2009). Currently, surgery is a common strategy for treatment of lung cancer, involving partial resection and total resection (Hennon and Demmy, 2012). During the surgery, surgical trauma, pains, anesthetic intubation and extubation may induce the potent stress response that may trigger the severe complications, affecting the surgical efficacy, prognosis and recovery of patients (Neal, 2009). In-time and effective methods to alleviate the stress response is significant for management of the intra- and postoperative complications and improvement of

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the prognosis. Midazolam, as a typical benzodiazepine anesthetics, can antagonize the anxiety and seizure, and also has the hypnotic, muscle-relaxing and sedative effect. Moreover, it can also free the patients from the painful memory of the surgery. Thus, it is frequently applied in the anesthesia induction in surgeries, including the surgery for lung cancer. However, how to precisely evaluate the dose of the anesthetics remains to be an issue in clinical research (Brummett et al., 2008; Ho and Ismail, 2008; Gao et al., 2017a,b, c). To provide the rational reference for the dose of midazolam for the patients to undergo the thoracoscopic resection of lung cancer, we analyzed the analgesic effect of midazolam in different dose on the patients who underwent the thoracoscopic resection of lung cancer.

1. Materials and methods

1.1. Clinical data

Ninety patients undergoing the thoracoscopic resection of lung cancer in this hospital between August 2017 and July 2018 were enrolled according to the following criteria. Inclusive criteria: (a) patients who volunteered to participate in this study; (b) patients who were diagnosed as the lung cancer by the laboratory examination and pathological biopsy after the surgery; (c) patients who gained the compliance and cooperated with the medical staff to fulfill this study; (d) patients who had no allergy. Exclusive criteria: (a) patients had the severe complications in heart or lung; (b) patients who had the obesity; (c) patients with the history of mental disorders, or cognitive dysfunction; (d) patients who failed to complete the examination as required, or received the treatment methods that might interfere on the outcome of this study. These patients were randomized to the observation group (n = 45) and the control group (n = 45). The observation group comprised 32 males (71.1%) and 13 females (28.9%), with an average age of (58.33 ± 2.45) years old; the control group consisted of 34 males (75.6%) and 11 females (24.4%), with an average age of (58.38 ± 2.49) years old. Differences regarding the gender, age, BMI and heart rates of patients between two groups were not significant ($P > 0.05$), showing that the data were comparable (Table 1). All patients participated in this study with the informed consent, and this study had been approved by the Ethical Committee of the hospital.

1.2. Anesthetic methods

All patients received the regular examinations of the blood pressure, heart rate and SaO_2, and the monitoring of the electrocardiogram, pulse, and bispectral index (BIS) immediately after entrance into the operation room. At the time of anesthetic induction, patients in the observation group took 0.1 mg/kg midazolam (Approval No.: SFDA H20067041; Manufacturer: Yichang Humanwell Pharmaceutical Co., Ltd; Specification: 2 mL: 10 mg), while those in the control group took 0.05 mg/kg midazolam. Meanwhile, all patients additionally took 0.15 mg/kg Cisatracurium Besilate (Approval No.: SFDA H20060927; Manufacturer: Dongying Pharmaceutical Co., Ltd, Shanghai Pharma; Specification: 5 mg), 4 μg/kg Fentanyl Citrate (Approval No.: SFDA H20113508; Manufacturer: Jiangsu Nhwa Pharmaceutical Co., Ltd.; Specification: 2 mL : 0.1 mg fentanyl), and 0.3 mg/kg Etomidate Fat Emulsion Injection (Approval No.: SFDA H20020511; Manufacturer: Jiangsu Nhwa Pharmaceutical Co., Ltd.; Specification: 10 mL:20 mg). At 5 min after induction, patients received the intubation, and following the guidance of the fiber bronchoscope, mechanical ventilation was performed with the airway pressure of one-lung ventilation at about 30 cmH_2O, and $PaCO_2$ at the end of breath at 30–40 mmHg. During the surgery, propofol (Approval No.: SFDA H20133360; Manufacturer: Guangdong Jiabo Pharmaceutical Co. Ltd; Specification: 50 mL: 500 mg) and remifentanil (Approval No.: SFDA H20143314; Manufacturer: Jiangsu Nhwa Pharmaceutical Co., Ltd.; Specification: 1 mg fentanyl) were infused to sustain the anesthesia, and the doses were adjusted in time, and intermittent infusion of Cisatracurium Besilate was performed to sustain the BIS index at 40–60. At 30 min prior to the end of surgery, muscle relaxant was withdrawn, and neostigmine (Approval No.: SFDA H31022770; Manufacturer: Shanghai Sine-Jinzhu Pharmaceutical Co., Ltd.; Specification: 2 mL: 1 mg) was given only after the restoration of autonomous respiration to antagonize the muscle relaxant. Immediately after the surgery, anesthetics were all withdrawn, and 0.5 mg flumazenil (Approval No.: SFDA H20066462; Manufacturer: Zhejiang Hisun Pharmaceutical Co., Ltd.; Specification: 5 mL: 0.5 mg) was infused to antagonize the residual midazolam.

1.3. Observation indexes

Levels of inflammatory factors before surgery and at 48 h following the surgery between two groups, were compared. In brief, 3 mL fasting venous blood was drawn from the patients before surgery and at 48 h after surgery, and the serum was isolated by centrifugation and preserved at −50 °C for examination. Enzyme-linked immunosorbent assay (ELISA) was applied to detect the inflammatory factors. Furthermore, we also monitored the SaO_2, average arterial pressure and heart rate of patients in two groups before surgery and at 48 h after surgery by using a multifunctional monitor.

Additionally, following indexes were also observed to evaluate the efficacy of surgery, including the bleeding amount, surgical time, anesthesia time, eye-opening time, extubation time, postoperative pain score and total dose of propofol and remifentanil. Besides, the visual analogue scale (VAS) was utilized to assess the postoperative pains with a score between 0 and 10 (0 for painless, and 10 for intolerable pains).

1.4. Statistical methods

Data in this study were processed using the SPSS 11.5. Measurement data, in form of mean ± standard deviation, were compared between two groups with the independent sample *t* test, and between different time points within one group with the pairwise sample *t* test. Enumeration data, in form of n (%), were compared

Table 1
The clinical data of patients in two groups.

Group	n	BMI (kg/m^2)	Heart beat (beat/min	Disease course (year)	ASA grade [n(%)]	
					Grade II	Grade III
Observation group	45	24.75 ± 1.32	73.31 ± 4.10	6.42 ± 0.24	33(73.33)	12(26.67)
Control group	45	24.73 ± 1.30	73.36 ± 4.14	6.48 ± 0.30	31(68.89)	14(31.11)
t/χ^2		0.284	0.107	0.966	0.237	
P		0.777	0.915	0.337	0.626	

using the chi-square test. $P < 0.05$ suggested the statistical significance of the difference.

2. Results

2.1. Comparison of the inflammatory factors between two groups before and after surgery

Before surgery, differences in the levels of inflammatory factors between two groups showed were not significant ($P > 0.05$), but at 48 h after surgery, a magnificent decrease was identified in two groups ($P < 0.05$), while the more magnificent decrease was identified in the observation group ($P < 0.05$; Table 2).

2.2. Comparison of the indexes between two groups before and after surgery

Before surgery, differences in the SaO_2, average arterial pressure and heart rate were not significant ($P > 0.05$), but at 48 h after surgery, magnificent increases were identified in two groups ($P < 0.05$), while the increases in the observation group were less evident ($P < 0.05$; Table 3).

2.3. Comparison of the surgical conditions between two groups

During the surgery, comparison of the bleeding amount, surgery time and anesthesia time between two groups showed that the differences were not significant ($P > 0.05$), but in the observation group, the eye-opening time and extubation time were shortened significantly ($P < 0.05$), while the postoperative pain score and the doses of the propofol and remifentanil were lowered ($P < 0.05$; Table 4).

3. Discussion

Midazolam, as the most common anesthetic induction drug in the general anesthesia, performs well in sedation, hypnosis, anti-anxiety, anti-seizure and muscle relaxing; moreover, it has the effect of anterograde amnesia, and, besides, helps patients avoid the inflammatory noxious stimulation during the surgery. Midazolam is dissolvable in water and rapidly metabolized, and after withdrawal, patients can rapidly recover from the anesthesia; thus, it is more applicable to sustain the anesthesia (Adnan et al., 2005; Tsubokura et al., 2016). Lung cancer patients, due to the weak renal and hepatic function caused by the disease progression, are vulnerable in metabolism of drugs, which may be exacerbated after the intravenous injection of midazolam. It is reported that midazolam usually results in the delayed recover and the cognitive dysfunction (Rutkowska et al., 2009; Kathuria et al., 2015). Excessive administration of midazolam may trigger the adverse reactions, including respiratory inhibition or delayed recover. Taken together, anesthetists usually take an extremely low dose of midazolam (0.05 mg/kg) for anesthetic induction (Agarwal et al., 2014). Nevertheless, patients who will undergo the thoracoscopic resection of lung cancer suffer from the horror and anxiety, and rational increase in the dose of midazolam may help the patients fall into sleep; sequentially, administration of other anesthetics can sustain the anesthesia efficiently (Abdallah et al., 2016; Purdy et al., 2016). In this study, we found that for the administration of midazolam at a dose of 0.1 mg/kg or 0.05 mg/kg, patients had no significant change in the anesthesia time, with a steady anesthetic effect, which might be correlated with BIS.

In this study, at the anesthetic induction, midazolam was given at different doses (0.1 mg/kg and 0.05 mg/kg), and with the real-time monitoring of the BIS, doses of midazolam and remifentanil were adjusted at any time during the surgery to sustain the BIS

Table 2
The inflammatory factors of patients in two groups before and after surgery ($\bar{x} \pm s$, μg/L).

Group	n	IL-6		*t*	*P*	IL-8		*t*	*P*
		Before surgery	At 48 h after surgery			Before surgery	At 48 h after surgery		
Observation group	45	153.22 ± 11.22	58.44 ± 3.22	52.045	0.000	4.22 ± 0.55	2.04 ± 0.26	23.457	0.000
Control group	45	153.19 ± 11.19	96.44 ± 4.534	30.123	0.000	4.26 ± 0.52	3.23 ± 0.33	10.953	0.000
t		0.011	43.824			0.344	18.763		
P		0.991	0.000			0.730	0.000		
Group	IL-1β		*t*	*P*	TNF-α		*t*	*P*	
	Before surgery	At 48h after surgery			Before surgery	At 48h after surgery			
Observation group	5.75±0.98	2.98±0.44	16.715	0.000	9.94±1.33	5.33±0.77	19.379	0.000	
Control group	5.76±0.96	3.77±0.44	12.218	0.000	9.95±1.36	7.64±0.99	8.866	0.000	
t	0.046	8.317			0.033	11.926			
P	0.964	0.000			0.974	0.000			

Table 3
SaO_2 and average arterial pressure in two groups before and after surgery ($\bar{x} \pm s$).

Group	n	SaO_2 (%)		*t*	*P*	Average arterial pressure (mmHg)		*t*	*P*
		Before surgery	At 48 h after surgery			Before surgery	At 48 h after surgery		
Observation group	45	90.23 ± 1.33	93.79 ± 1.08	2.555	0.014	80.44 ± 2.99	93.22 ± 3.46	17.949	0.000
Control group	45	90.32 ± 1.29	97.13 ± 1.03	5.191	0.000	80.22 ± 3.05	96.44 ± 4.03	20.606	0.000
t		0.016	2.566			0.330	3.891		
P		0.987	0.013			0.741	0.000		
Group	Heart (beat/min)					*t*		*P*	
	Before surgery		At 48h after surgery						
Observation group	80.22±4.23		87.55±2.35			9.726		0.000	
Control group	80.25±4.24		91.05±2.89			3.513		0.000	
t	0.031		6.038						
P	0.975		0.000						

Table 4
Comparisons of the surgical condition between two groups ($\bar{x} \pm s$).

Group	n	Bleeding amount (mL)	Surgery time (min)	Anesthesia time (min)	Eye-opening time (min)	Extubation time (min)
Observation group	45	256.33 ± 21.44	142.33 ± 10.55	146.44 ± 12.12	6.04 ± 1.13	9.88 ± 1.43
Control group	45	257.02 ± 21.53	143.42 ± 10.63	145.42 ± 12.10	13.88 ± 1.35	21.77 ± 1.92
t		0.145	0.466	0.381	28.744	31.907
P		0.886	0.643	0.705	0	0

	Postoperative pains scores	Total dose of propofol (mL)	Total dose of remifentanil (mg)
Observation group	1.44±0.22	71.22±5.68	2.33±0.27
Control group	2.52±0.29	93.44±6.15	3.72±0.36
t	19.757	17.023	20.412
P	0.000	0.00	0.000

within 40 and 60 to free the patients from the harmful memory of surgery and keep them safe. Prior to the anesthetic induction, discomfort of patients was mitigated maximally by smearing the lidocaine cream evenly on the surface of the urinary catheter and tracheal catheter. Furthermore, patients who took 0.1 mg/kg midazolam had a lower postoperative pain score, and the total doses of the propofol and remifentanil than those taking 0.05 mg/kg, and this is possibly because a higher dose of midazolam may reduce the doses of other anesthetics as well as the pain score (Chen et al., 2016; He et al., 2011). Additionally, we also found that patients who took 0.1 mg/kg midazolam for anesthesia induction had shorter postoperative eye-opening time and extubation time than those taking 0.05 mg/kg midazolam. Since the patients took a lower dose of midazolam, higher doses of fentanyl and remifentanil are required to sustain the BIS within 40 and 60. Additionally, the poor metabolism of elder patients may prolong the eye-opening time and extubation time. In this study, we also found that before surgery, there were no differences between the SaO_2, average arterial and heart rate between two groups, and though patients had slight increases in SaO_2, average arterial and heart rate at 48 h after the anesthetic induction through 0.1 mg/kg midazolam, increases remained lower than those of patients who took 0.05 mg/kg midazolam, suggesting that midazolam at a higher dose may inhibit the stress responses of patients.

As the stress responses of patients come with the immune responses, inflammatory cytokines are massively released (Kamiyoshihara et al., 2011; Kumar et al., 2017). These cytokines mediate a variety of the inflammatory responses, severely affecting the health of patients, or even inducing the multi-organ failure or general inflammatory responses (Aigner et al., 2003; Hussain et al., 2017). In this study, after the anesthetic induction by 0.1 mg/kg for patients to undergo the thoracoscopic resection of lung cancer, the levels of inflammatory factors were reduced, while the decreases in the observation group were more magnificent in comparison with those taking 0.05 mg/kg midazolam, indicating that midazolam at a higher dose can effectively lower the levels of inflammatory factors of patients.

Overall, anesthetic induction by 0.1 mg/kg midazolam for patients who undergo the thoracoscopic resection of lung cancer can better inhibit the inflammatory responses of patients than 0.05 mg/kg midazolam, with remarkable decreases in doses of anesthetics, steady perioperative period and effective relief in postoperative pains. Thus, this is an ideal protocol for anesthesia.

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