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

Lixia Zhang a,1, Gang Wang b,1, Jianhui Gan c,1, Zhongci Dou a, Liying Bai a,1,*

a Department of Anesthesiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450000, China
b Department of Anesthesiology, Tianjin First Central Hospital, Tianjin 300190, China
c Department of Anesthesiology, The Affiliated Tangshan People's Hospital of North China University of Science and Technology, Tangshan 063000, China

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, SaO2, 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-1b and TNF-a: (58.44 ± 3.22) lg/L, (2.04 ± 0.26) lg/L, (2.98 ± 0.44) lg/L, (5.33 ± 0.77) lg/L v.s. (96.44 ± 4.54) lg/L, (3.23 ± 0.33) lg/L, (3.77 ± 0.44) lg/L, (7.64 ± 0.99) lg/L] (P < 0.05). Meanwhile, those in the observation group had a lower SaO2, 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.

© 2019 Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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 SaO2, 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 H200670741; 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 cmH2O, and PaCO2 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 SaO2, 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/m²) | Heart beat (beat/min) | Disease course (year) | ASA grade [n(%)] |
|----------------|----|-------------|-----------------------|-----------------------|-----------------|
|                |    |             |                       |                       | Grade II | Grade III |
| Observation     | 45 | 24.75 ± 1.32| 73.31 ± 4.10          | 6.42 ± 0.24           | 33(73.33) | 12(26.67) |
| Control         | 45 | 24.73 ± 1.30| 73.36 ± 4.14          | 6.48 ± 0.30           | 31(68.89) | 14(31.11) |
| t/x²            |    | 0.284       | 0.107                 | 0.966                 | 0.237    | 0.626    |
| 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 magnificient decrease was identified in two groups \( (P < 0.05) \), while the more magnificient decrease was identified in the observation group \( (P < 0.05; \text{Table 2}) \).

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

Before surgery, differences in the \( \text{SaO}_2 \), average arterial pressure and heart rate were not significant \( (P > 0.05) \), but at 48 h after surgery, magnificient increases were identified in two groups \( (P < 0.05) \), while the increases in the observation group were less evident \( (P < 0.05; \text{Table 3}) \).

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 \( (P < 0.05; \text{Table 4}) \).

### Table 2

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

| Group                  | n   | IL-6 Before surgery | t   | P   | IL-6 At 48 h after surgery | tP   | IL-8 Before surgery | t   | P   | IL-8 At 48 h after surgery | tP   |
|------------------------|-----|---------------------|-----|-----|----------------------------|------|---------------------|-----|-----|----------------------------|------|
| Observation group      | 45  | 153.22 \( \pm \) 11.22 | 58.44 \( \pm \) 3.22 | 52.045 | 0.000                   | 4.22 \( \pm \) 0.55 | 2.04 \( \pm \) 0.26 | 23.457 | 0.000 |
| Control group          | 45  | 153.19 \( \pm \) 11.19 | 96.44 \( \pm \) 4.534 | 30.123 | 0.000                   | 4.26 \( \pm \) 0.52 | 3.23 \( \pm \) 0.33 | 10.953 | 0.000 |
| t                      | 0.011 | 43.824             | 0.991 | 0.000 |
| p                      | 0.344 | 18.763             | 0.730 | 0.000 |

### Table 3

\( \text{SaO}_2 \) and average arterial pressure in two groups before and after surgery (\( \bar{x} \pm s \)).

| Group                  | n   | \( \text{SaO}_2 \) (%) Before surgery | t   | P   | \( \text{SaO}_2 \) (%) At 48 h after surgery | t  | Average arterial pressure (mmHg) Before surgery | t   | P   | Average arterial pressure (mmHg) At 48 h after surgery | t   | P   |
|------------------------|-----|-------------------------------------|-----|-----|---------------------------------------------|----|-----------------------------------------------|-----|-----|---------------------------------------------|-----|-----|
| Observation group      | 45  | 90.23 \( \pm \) 1.33               | 93.79 \( \pm \) 1.08 | 2.555 | 0.014                   | 80.44 \( \pm \) 2.99 | 93.22 \( \pm \) 3.46 | 17.949 | 0.000 |
| Control group          | 45  | 90.32 \( \pm \) 1.29               | 97.13 \( \pm \) 1.03 | 5.191 | 0.000                   | 80.22 \( \pm \) 3.05 | 96.44 \( \pm \) 4.03 | 20.606 | 0.000 |
| t                      | 0.016 | 2.566                 | 0.987 | 0.013 |
| p                      | 0.741 | 3.891                 | 0.741 | 0.000 |

### Table 3 Continued

| Group                  | n   | Heart (beat/min) Before surgery | t   | P   | Heart (beat/min) At 48 h after surgery | t   | P   |
|------------------------|-----|---------------------------------|-----|-----|---------------------------------------|-----|-----|
| Observation group      | 45  | 80.22 \( \pm \) 4.23             | 87.55 \( \pm \) 2.35 | 9.726 | 0.000 |
| Control group          | 45  | 80.25 \( \pm \) 4.24             | 91.05 \( \pm \) 2.89 | 3.513 | 0.000 |
| t                      | 0.031 | 6.038                 | 0.975 | 0.000 |

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.
Comparisons of the surgical condition between two groups (x ± s).

| Group         | n  | Bleeding amount (mL) | Surgery time (min) | Anesthesia time (min) | Eye-opening time (min) | Extubation time (min) |
|---------------|----|----------------------|--------------------|-----------------------|------------------------|------------------------|
| Observation   | 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             | 0.14 | 0.46                | 0.381              | 28.744                | 0                      | 31.907                 |
| P             | 0.886 | 0.643              | 0.705              | 0                     | 0                      | 0                      |

Postoperative pains scores

| Group         | n  | Postoperative pains scores | Total dose of propofol (mL) | Total dose of remifentanil (mg) |
|---------------|----|-----------------------------|-----------------------------|---------------------------------|
| Observation   | 1.44±0.22 | 71.22±5.68                 | 2.335±0.27                  |                                 |
| Control group | 2.52±0.29 | 93.44±6.15                 | 3.720±3.06                  |                                 |
| t             | 19.757 | 17.023                      | 20.412                      |                                 |
| P             | 0.00 | 0.00                        | 0.00                        |                                 |

Adnan, T., Elif, A.A, Ayse, K., Gulnaz, A., 2005. Clonidine as an adjuvant for lidocaine in axillary brachial plexus block in patients with chronic renal failure. Acta Anaesthesiol. Scand. 49, 563–568.

Agarwal, S, Aggarwal, R., Gupta, P., 2014. Dexmedetomidine prolongs the effect of bupivacaine in supraclavicular brachial plexus block. J. Anaesthesiol. Clin. Pharmacol. 30, 36–40.

Aigner, C., Jakobsch, P., Seebacher, G., 2003. Single running suture—the new standard technique for bronchial anastomoses in lung transplantation. Eur. J. Cardiothorac. Surg. 23, 488–493.

Brummett, C.M., Norat, M.A., Palmsino, J.M., Lydic, R., 2008. Perineural administration of dexmedetomidine in combination with bupivacaine enhances sensory and motor blockade in sciatic nerve block without inducing neurotoxicity in rat. Anesthesiology 109, 502–511.

Chen, C., L., Lyu, L., Long, C., et al., 2016. Effects of circuit albumin coating on coagulation and inflammatory response for patients receiving aortic arch replacement: a randomized controlled trial. Pulsion 31 (7), 576–583.

Gao, W., Baig, A.Q., Ali, H., Sajjad, W., Farahani, M.R., 2017a. Margin based ontology sparse vector learning algorithm and applied in biology science. Saudi J Biol Sci. 24, 132–138.

Gao, W., Wang, Y., Basavanagoud, B., Jamil, M.K., 2017b. Characteristics studies of molecular structures in drugs. Saudi Pharm J. 25, 580–586.

Hennen, M.W., Denmy, T.L., 2012. Video-assisted thoracoscopic surgery (VATS) for locally advanced lung cancer. Ann. Cardiothorac. Surg. 1, 37–42.

Ho, K.M., Ismail, H., 2008. Use of intrathoracic midazolam to improve perioperative analgesia: a meta-analysis. Anesth. Intens. Care 36, 365–373.

Kamiyoshihara, M., Nagashima, T., Igai, H., 2011. Video-assisted thoracic lobectomy with bronchoplasty for lung cancer, with special reference to methodology. Interact. Cardiovasc. Thorac. Surg. 12, 534–538.

Katheria, S., Gupta, S., Dhanwan, I., 2015. Dexmedetomidine as an adjuvant to ropivacaine in supraclavicular brachial plexus block. J. Anaesth 9, 148–154.

Kumar, A., Sinha, C., Kumar, A., Kumar, P., 2017. The effect of intravenous dexmedetomidine compared to propofol on patients hemodynamics as a sedative in brachial plexus block: a comparative study. Anesth. Essays Res. 11, 201–205.

McKenna, R.J., Houck, W., Fuller, C.B., 2006. Video-assisted thoracic surgery lobectomy: experience with 1100 cases. Ann. Thorac. Surg. 81, 421–425.

Neal, J.M., 2009. The upper extremity: somatic block. In: Cousins, M.J., Horlocker, T. T., Riberbauh, P.O., Carr, D.B. (Eds.), Neural Blockade in Clinical Anesthesia and Pain Medicine. Fourth ed. Lippincott Williams & Wilkins, Philadelphia, pp. 316–342.

Purdy, M., Kokki, M., Antilla, M., et al., 2016. Does the rectus sheath block analgesia reduce the inflammatory response biomarkers IL-1ra, IL6, IL-8, IL-10 and IL-17 concentrations following surgery? A randomized clinical trial of patients with cancer and benign disease. Anticancer. Res. 36 (6), 3005–3011.

Rashid, O.M., Takabe, K., 2012. Are video-assisted thoracoscopic surgery (VATS) and robotic video-assisted thoracic surgery (RVATS) for pulmonary resection ready for prime time? J. Thorac. Dis. 4, 341–342.

Rutkowska, K., Knapik, P., Misiolek, H., 2009. The effect of dexmedetomidine sedation on brachial plexus block in patients with end-stage renal disease. Eur. J. Anaesthesiol. 26, 851–855.

Tsubokura, Y., Kobayashi, T., Oshima, Y., et al., 2016. Effects of pentobarbital, isoflurane, or medetomidine-midazolam-butorphanol anesthesia on bronchoalveolar lavage fluid and blood chemistry in rats. J. Toxicol. Sci. 41 (5), 595–604.

Villamizar, N.R., Darrabie, M.D., Burfeind, W.R., 2009. Thoracoscopic lobectomy is associated with lower morbidity compared with thoracotomy. J. Thorac. Cardiovasc. Surg. 138, 419–425.

References

Abdallah, F.W., Dwyer, T., Chan, V.W., Niazi, A.U., Ogilvie-Harris, D.J., Oldfield, S., et al., 2016. IV and perineural dexmedetomidine similarly prolong the duration of analgesia after intercalane brachial plexus block: a randomized, three-arm, triple-masked, placebo-controlled trial. Anesthesiology 124, 683–695.