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Prospective analysis of efficacy and safety of an individualized-midazolam-dosing protocol for sedation during prolonged bronchoscopy

Tomomi Ogawa[a,1], *Kazuyoshi Imaizumi*[b,*], *Izumi Hashimoto*[b], *Yuichiro Shindo*[a], *Naoyuki Imai*[a], *Sakurako Uozu*[b], *Tomoya Shimokata*[a], *Satoru Ito*[a], *Naozumi Hashimoto*[a], *Mitsuo Sato*[a], *Masashi Kondo*[a], *Yoshinori Hasegawa*[a]

[a]*Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[b]*Division of Respiratory Medicine and Clinical Allergy, Department of Internal Medicine, Fujita Health University, Toyoake, Aichi 470-1192, Japan*

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ABSTRACT

Background: Newer more advanced techniques in bronchoscopy may require longer procedure times, although a standard protocol for sedation during prolonged bronchoscopy has not yet been defined.

Methods: We designed a prospective, non-randomized, single-arm study (UMIN trial number 000003971) using patient questionnaires and vital sign monitoring to assess the efficacy and safety of a standardized midazolam dosing protocol based on gender and age for use during bronchoscopy. The loading dose of midazolam was 0.075 mg/kg for men $\leq$ 65 years old and women $\leq$ 70 and 0.05 mg/kg for men $\geq$ 66 years and women $\geq$ 71 years, with subsequent doses of one-half the loading dose to be administered every 20 min. The primary endpoint was tolerability and secondary endpoints included anxiety and recall of procedure, willingness to undergo repeat procedure, and complications. Safety was evaluated in terms of monitored changes in blood pressures, ECG, oxygen saturation, and CO_2 content in expiration during the procedure.

Results: A total of 204 patients were included in the study. Overall, 163 patients (79.9%) reported "no distress" during the procedure, 185 patients (90.7%) reported "no anxiety," and 175 (85.8%) replied that they would accept a repeat procedure, if necessary. The mean minimum oxygen saturation was 90.2% and the mean maximum expiratory CO_2 level was 37.7 mmHg. There were no serious complications related to the protocol.

Abbreviations: EBUS, endobronchial ultrasound; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EBUS-GS, endobronchial ultrasonography with a guide sheath; BAL, bronchoalveolar lavage; TBNA, transbronchial needle aspiration

*Corresponding author. Tel.: +81 562 93 9241; fax: +81 562 93 3576.
E-mail addresses: tomomi.ogawa0616@gmail.com (T. Ogawa), jeanluc@fujita-hu.ac.jp (K. Imaizumi), izumi-hashimoto@gate.sws.co.jp (I. Hashimoto), yshindo@med.nagoya-u.ac.jp (Y. Shindo), naoi6014@med.nagoya-u.ac.jp (N. Imai), suozu@med.nagoya-u.ac.jp (S. Uozu), tshimo@med.nagoya-u.ac.jp (T. Shimokata), itori@med.nagoya-u.ac.jp (S. Ito), hashinao@med.nagoya-u.ac.jp (N. Hashimoto), msato@med.nagoya-u.ac.jp (M. Sato), mkond@med.nagoya-u.ac.jp (M. Kondo), yhasega@med.nagoya-u.ac.jp (Y. Hasegawa).
[1]*Present address*: Department of Respiratory Medicine, Tsushima Municipal Hospital, Tsushima, Japan.

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Conclusions: The midazolam dosing protocol examined in this study was safe and effective. It is simple, and it could easily be translated to routine clinical practice.

1. Introduction

Flexible bronchoscopy is frequently used for the diagnosis or management of pulmonary disorders. In order to minimize patient discomfort, sedation is recommended when there is no contraindication [1]. The ideal sedative will be safe, easy to use, effective, and economical. Several trials have been conducted to determine the best sedation methods for patients undergoing bronchoscopy [2,3], and benzodiazepines such as midazolam, opioids, and propofol or fospropofol (a prodrug of propofol) have all been recommended [4–6], but no standard protocol has been established, and neither ideal initial doses nor timing of additional doses have been specified. The advanced techniques and equipment that have been introduced to the field of respiratory endoscopy, including endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and EBUS-guided transbronchial lung biopsy [7], have allowed greater diagnostic yield, but they are more complicated and may require longer examination times [8]. Thus, it is important to determine the most suitable sedation methods for bronchoscopic procedures. The short-acting benzodiazepine midazolam is one of the most commonly used sedatives, and it has been proven safe even for patients with stable respiratory failure [9]. Various reports and international guidelines have recommended initial doses of midazolam ranging from 0.07 mg/kg to 0.67 mg/kg [1] and have also demonstrated that 2 mg/body of midazolam with or without opiates is sufficient for initial sedation during bronchoscopy. Although there is still no standardized method for incremental dosing of midazolam, it is recognized that incremental dosing is required because sufficient sedation usually will not be achieved by a single dose [1]. In previous trials, additional injections of midazolam have been administered according to the operator's discretion, based mainly on the assessment of patient's condition [1,9]. This method carries a risk of overdose. In addition, it may be difficult to ensure effective sedation in the absence of an established protocol during routine clinical practice. The bispectral index (BIS) and the observer assessment of alertness/sedation score (OAA/S) are both used for assessing levels of sedation [10]. The BIS is largely non-invasive and is a useful indicator of the depth of anesthesia during bronchoscopy, but it requires electroencephalography (EEG) and electromyography (EMG) data, which may limit its availability in the daily clinical setting. We conducted a pilot study (unpublished data) examining the efficacy of midazolam sedation during bronchofiber examination at our institution in which we administered a single dose of 0.05 mg/kg midazolam at the start of the examination without any additional injections. We found that patients had significantly increased discomfort and anxiety levels when the examination lasted longer than 20 min, and we discovered that male patients younger than 66 years and female patients younger than 71 years experienced greater discomfort than older patients. Thus, we determined that midazolam dose should be adjusted based on sex and age. It was under these circumstances that we proposed a simple method of midazolam administration using individualized (mg/kg) metered initial doses and timed additional dosages for sedation during bronchoscopy. The current study was performed to assess the efficacy and safety of this protocol.

2. Materials and methods

2.1. Study design

This was a prospective, non-randomized, single-center study (trial number: UMIN 000003971). The Nagoya University Hospital Institutional Review Board approved the protocol (Nagoya University approval no. 908-2, approval date; May 21, 2010). The study was performed in accordance with the ethical standards of the Declaration of Helsinki. All patients provided written informed consent.

2.2. Patients

Consecutive patients ≥ 20 years of age who underwent diagnostic bronchoscopy in Nagoya University Hospital between July 2010 and March 2011 were enrolled in the study. Patients with an American Society of Anesthesiologists (ASA) Physical Classification System status of P1 to P3 were eligible. The criteria for patient eligibility also included the ability to answer a simple questionnaire without assistance; adequate hepatic function (AST ≤ 100 IU/L, ALT ≤ 100 IU/L, and total bilirubin ≤ 1.5 mg/dL); adequate renal function (serum creatinine ≤ 1.5 mg/dL); and adequate respiratory function ($PaO_2 \geq 60$ mmHg or $SaO_2 \geq 90\%$ while breathing room air). Exclusion criteria included chronic respiratory failure with $SpO_2 < 90\%$ (room air at rest); type II chronic respiratory failure requiring long-term oxygen therapy (LTOT); sleep apnea syndrome requiring constitutive positive airway pressure assistance; history of severe drug allergy including hypersensitivity to midazolam; neuromuscular disorders; acute narrow-angle glaucoma; myocardial infarction onset within 6 weeks; and pregnant or lactating women.

2.3. Study endpoints

The primary endpoint was the level of discomfort during bronchoscopy (no distress, some distress, extreme distress) as reported by each patient by using a categorized questionnaire prepared for the study. The secondary endpoints included anxiety level and extent of recall of the bronchoscopy, willingness to repeat flexible bronchoscopy, and complications