Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Original article

Patient-oriented optimal depth of conscious sedation using midazolam during flexible bronchoscopy: A prospective open-labeled single-arm trial ☆

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ARTICLE INFO

Article history:
Received 18 September 2017
Received in revised form
12 March 2018
Accepted 30 March 2018

Keywords:
Conscious sedation
Flexible bronchoscopy
Optimal depth
Ramsay sedation score

ABSTRACT

Background: The British Thoracic Society guidelines for diagnostic flexible bronchoscopy (FB) in adults recommend that intravenous sedation should be offered to patients undergoing bronchoscopy. However, it is difficult to determine the adequate depth of sedation for each patient because of inter-individual variability.

Methods: This prospective, open-label, single-arm study was conducted in patients undergoing routine bronchus examination with FB. All patients underwent FB under local anesthesia and conscious sedation, with initial administration of 0.03 mg/kg midazolam. The sedation level during FB was objectively assessed using the Ramsay sedation score (RSS). Two hours after the procedure, patients completed a questionnaire about its efficacy and adverse effects using a visual analog scale (VAS). Receiver operating characteristic (ROC) curve analyses were performed to determine the optimal RSS that could improve the subjective efficacy indicated by the VAS.

Results: This study enrolled 110 consecutive patients between September 2008 and February 2012. The median total amount of midazolam administered was 1.65 mg per patient. In an analysis of ROC curves between RSS and VAS, the area under the ROC curve for an RSS of 4 against the others was 0.66 (95% CI: 0.54 to 0.77, $p = 0.014$). The area under the ROC curve was not shown to be statistically significant for RSSs other than 4.

Conclusions: The optimal depth of conscious sedation during FB for conventional examination was achieved at an RSS of 4. The patients' subjective evaluations indicated that a deep level of conscious sedation does not seem necessary for FB.

Abbreviations: AUC_{RSS}, area under the Ramsay sedation score curve; AUC_{RSS}/m, area under the Ramsay sedation score curve per minute; AUC_{ROC}, area under the receiver operating characteristic curve; BTS, British Thoracic Society; FB, flexible bronchoscopy; IBW, ideal body weight; RSS, Ramsay sedation score; RSS/m, RSS per minute; ROC, receiver operating characteristic; VAS, visual analog scale; EBUS-GS, endobronchial ultrasonography with a guide sheath; EBUS-TBNA, endobronchial ultrasonography with transbronchial needle aspiration

☆Trial registration: University Hospital Medical Information Network (UMIN) - Clinical Trials Registry UMIN000005547.

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https://doi.org/10.1016/j.resinv.2018.03.007
2212-5345/

1. Introduction

Flexible bronchoscopy (FB) is now widely used for the diagnosis and treatment of pulmonary diseases. Intravenous sedation is frequently employed to improve patient comfort during FB in North America and Europe [1]. A 2010 report by the Japan Society for Respiratory Endoscopy revealed that intravenous sedatives were still used in only 36.1% of the facilities in Japan, although their usage has been gradually increasing [2]. The British Thoracic Society (BTS) guidelines for diagnostic FB recommend that sedation should be offered to patients and that sedatives should be used in incremental doses to achieve adequate sedation and amnesia [1]. The 2013 BTS guidelines also mention that the desired depth of sedation is usually "conscious" sedation. However, there are few reports evaluating the optimal depth of sedation during FB [3–5]. Most studies have not evaluated the optimal depth of sedation [3–5] because of inter-individual variability.

The purpose of this study was to determine the optimal depth of conscious sedation after intravenous administration of midazolam during FB, in order to improve patients' subjective satisfaction, comfort, and safety.

2. Patients and methods

2.1. Study design and patients

In this exploratory, prospective, open-label, single-arm study, the planned sample size was more than 100 patients, because it was calculated that 100 patients would have to be evaluated in the exploratory setting between September 2008 and February 2012. The study protocol was approved by our institutional ethics committee on June 26, 2008 (approval no. 523). This study was registered with University Hospital Medical Information Network - Clinical Trials Registry (UMIN000005547) on May 6, 2011.

The inclusion criteria were as follows: (1) FB for routine central bronchus examination; (2) age equal to or more than 20 years; (3) Eastern Cooperative Oncology Group performance status of 0 to 3; (4) adequate respiratory function ($pO_2 \geq 70$ Torr; $pCO_2 \leq 50$ Torr), cardiac function (brain natriuretic peptide level ≤ 150 pg/ml; ejection fraction in echocardiography $\geq 50\%$), hepatic function (bilirubin level ≤ 3.0 mg/dL; transaminase levels $< 2 \times$ the upper limit of the normal range), and renal function (creatinine level < 2.0 mg/dL or creatinine clearance ≥ 50 mL/min), and (5) informed consent. Exclusion criteria were as follows: 1) FB for a therapeutic procedure; 2) a history of hypersensitivity or allergy to anesthetic drugs or benzodiazepines; 3) any contraindications to midazolam; 4) uncontrolled comorbid diseases involving any of the following systems: respiratory (bronchial asthma, chronic obstructive lung disease, and respiratory failure), cardiac (angina pectoris, myocardial infarction, cardiac failure, arrhythmias), renal (renal failure with dialysis), neurological (cerebral vascular disorder), and hepatic (Child classification C with liver cirrhosis, fulminant hepatitis, liver failure); 5) pregnancy or lactation; 6) psychological disorders resulting in inability to give consent; 7) human immunodeficiency virus infection; 8) any other condition judged by bronchoscopy specialists as being unsuitable for inclusion.

Table 1 – Ramsay sedation score (RSS).

Score	Definition
1	Patient is **anxious** and **agitated** or **restless**, or both
2	Patient is **co-operative**, oriented, and tranquil
3	Patient **responds to commands** only
4	Patient exhibits **brisk response** to light glabellar tap or loud auditory stimulus
5	Patient exhibits a **sluggish response** to light glabellar tap or loud auditory stimulus
6	Patient exhibits **no response**

Adapted from Ramsay et al [6].

2.2. Procedures

Patients received premedication with 25 mg hydroxyzine hydrochloride intramuscularly, 0.5 mg atropine intramuscularly if indicated, and a 2% lidocaine gargle. During bronchoscopy, topical anesthesia was administered by transtracheal injection of 1% to 2% lidocaine, and the total amount administered was recorded. Tracheal intubation was not performed. Each patient was given intravenous fluids, such as lactated Ringer's solution, at a rate of 75 mL/h via an electronic infusion pump.

The midazolam dose as calculated below was administered by slow intravenous injection over 2 min through an intravenous cannula. Intravenous conscious sedation was initially achieved with 0.03 mg of midazolam per kilogram body weight using either actual or ideal body weight (IBW), whichever was lower. IBW was calculated using a body mass index value of 22 [22 × height (m) × height (m)]. If the patient was judged as being aware during the procedure, additional administration of 0.015 mg/kg midazolam was allowed via slow intravenous injection over 2 min. All patients were monitored using continuous pulse oximetry and electrocardiogram, as well as non-invasive blood pressure monitoring every 5 min. When desaturation below 90% occurred, supplemental oxygen was administered.

2.3. Evaluation

The level of sedation was evaluated using the Ramsay sedation score (RSS) [6] during the procedure (Table 1). The duration of the procedure was recorded as the period from the start to the end of FB.

One of the bronchoscopists played a role as the proceduralist for administered sedation and assessed the sedation level at 3–5 min after the initial injection of midazolam, at the beginning of FB, and then every 3–5 min during FB until the end of the procedure. We assessed the initial sedation level, maximal level of sedation achieved, as well as the sedation level at the end of the procedure. The area under the RSS curve (AUC_{RSS}) was evaluated using the trapezoidal rule (the RSS from the beginning to the end of the procedure). The AUC_{RSS} per minute (AUC_{RSS}/m) was defined as AUC_{RSS} divided by the procedure duration in minutes. The AUC_{RSS}/m was interpreted and defined as the RSS per minute (RSS/m). In this study, an RSS/m of 1, 2, 3, 4, and 5 was defined by a score of < 1.5, 1.5 to < 2.5, 2.5 to < 3.5, 3.5 to < 4.5, and ≥ 4.5, respectively.

Please cite this article as: Takeda Y, et al. Patient-oriented optimal depth of conscious sedation using midazolam during flexible bronchoscopy: A prospective open-labeled single-arm trial. Respiratory Investigation (2018), https://doi.org/10.1016/j.resinv.2018.03.007