Prospective Randomized Trial of Bispectral Index Monitoring of Sedation Depth during Flexible Bronchoscopy

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Abstract

Background: The clinical benefits associated with the use of the bispectral index (BIS) to monitor the depth of sedation during flexible fiberoptic bronchoscopy (FFB) are questionable. ***Objectives:*** To evaluate the added value in terms of procedural safety and patients' awareness of monitoring sedation depth using the BIS compared to conventional clinical judgment alone in patients undergoing FFB under propofol sedation. ***Methods:*** The cohort included 81 patients undergoing diagnostic or therapeutic bronchoscopy under propofol sedation that were prospectively randomized to guide the depth of sedation by BIS monitoring (BIS group; n = 40) or conventional monitoring (control group; n = 41). ***Results:*** The mean durations of the procedure were 18 and 19 min in the BIS and control groups, respectively. No significant difference was noted in the dosage of propofol used between the BIS and control groups (168.7 vs. 167.3 mg, respectively). Average sedation-related oxygen saturation drop and transcutaneous CO_2 rise were not significantly different between groups. There was also no significant difference in the percentage of patients that required either hemodynamic support (5 vs. 7.5%, respectively), oxygen supplementation by 100% O_2 mask (67.5 vs. 82.5%, respectively) or Ambu face mask manual ventilation (2.5 vs. 5%, respectively) between the groups. No significant difference was noted in terms of patients' awareness during the procedure, which was assessed following recovery by a structured Brice interview. ***Conclusion:*** Using BIS to guide the depth of sedation during propofol sedation in patients undergoing FFB of relatively short duration offers no clinically significant advantages over conventional monitoring.

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Introduction

Flexible fiberoptic bronchoscopy (FFB) is commonly used for the diagnosis and management of a variety of lung diseases. Although it may be performed with local anesthesia only, the addition of sedation can facilitate the examination of the tracheobronchial tree, lessen untoward physiologic responses to airway manipulation, diminish patient movement, and improve patient safety and comfort [1–4].

Recently, sedation with propofol for FFB has gained popularity, and randomized studies comparing propofol and midazolam sedation during FFB suggested a similar efficacy but faster onset of action and a more rapid patient recovery for propofol [5–8].

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Due to the risk of bradycardia, hypotension and respiratory depression associated with the use of pharmacological sedatives, in particular propofol, patients should be appropriately monitored with the continuous measurement of pulse rate and oxygen saturation with or without the use of transcutaneous PCO_2 monitoring ($TcCO_2$) and frequent measurements of blood pressure [9, 10].

To achieve the required level of sedation, the chosen pharmacological sedative should be administered by titration of small incremental doses to the desired clinical and physiological effect, irrespective of the route of administration, e.g. boluses or continuous infusion. The depth of sedation is traditionally monitored throughout the procedure and documented using the 5-grade observer assessment of alertness/sedation (OAA/S) score [11]. For moderate sedation, the depth of sedation should not be greater than that of level 3. Bispectral index (BIS) monitoring is an electroencephalographic (EEC)-based method [12, 13] to assess the patient's level of consciousness and may aid in monitoring the depth of anesthesia or sedation. Whereas the advantages of using BIS to monitor general anesthesia are relatively accepted by anesthesiologists, the benefits of using of BIS during moderate sedation are not well established. For example, a recent prospective randomized trial failed to detect clinically significant advantages of BIS compared to conventional monitoring in patients undergoing upper gastrointestinal endoscopy under propofol sedation [14].

Two trials of moderate sedation for bronchoscopy using BIS monitoring [15, 16] concluded that BIS can be used safely by the non-anesthetist to titrate sedation with propofol. However, in both of these carefully designed trials, BIS was used only in the propofol arm, whereas different sedative agents (midazolam and opiates) were used in the conventional monitoring arm. Hence, based on current available data, it is not clear whether the use of BIS monitoring offers significant advantages over the use of clinical judgment alone.

Consequently, we designed a prospective randomized trial in which all patients undergoing FFB were sedated by propofol and the only difference between study groups was the use of BIS compared to conventional monitoring.

Methods

This prospective, randomized study was conducted in a tertiary, university-affiliated, medical center between March 2012 and January 2013. The study cohort consisted of 81 patients scheduled for FFB under local anesthesia with sedation at a tertiary medical center. All patients provided written informed consent for bronchoscopy and participation in the study, which has been approved by the local ethics committee (Institutional Review Board approval 6633, ClinicalTrials.gov identifier: NCT01592513). Exclusion criteria for the study were inability or refusal to provide informed consent, age <18 years, bronchoscopy through an artificial airway, such as an endotracheal tube or tracheostomy, and allergy to propofol.

All the procedures were performed by either O.F. or M.R.K. to prevent inherent differences of skills among operators. A single anesthesiologist (M.T.), who was present in all the procedures, titrated sedation depth and administered sedation medications. An independent anesthesiologist was a member of the committee of the Institutional Review Board that approved the study.

Randomization and Blinding
Patients were randomly assigned by a computer-based software (GraphPad Software) before the procedure to receive sedation titration by BIS (BIS group) or by clinical judgment (control group). Both the patient and the operator who performed the bronchoscopy procedure were unaware of the subgroup to which the patient was allocated. The anesthesiologist who attended each of the procedures and monitored sedation depth was not blinded.

Titration of Sedation
During the procedure, the level of sedation was evaluated according to one of the following two ways.
Clinical Sedation Titration (Control Group). We applied the OAA/S scale: 1 = deep sedation, 2–4 = conscious sedation and 5 = mild sedation. The OAA/S score is calculated as follows: 5 = appropriate verbal response to the patient's name; 4 = lethargic response; 3 = response only after the patient's name is spoken loudly and/or repeatedly; 2 = response after mild prodding or shaking; 1 = response after painful stimuli, and 0 = no response at all).
BIS-Driven Sedation Titration (BIS Group). After cleansing the skin with gauze and alcohol, we applied disposable electrodes to the forehead and connected the leads to a BIS monitor (A-2000 BIS XP; Aspect Medical Systems, Newton, Mass., USA). The BIS monitor output was evaluated continuously throughout the procedure and recovery period. BIS ≤65 indicates deep sedation, 66–85 indicates conscious sedation, and BIS >85 indicates mild sedation [13, 14].

Sedation Protocol
Local anesthesia was induced by application of 2% lidocaine to the oropharynx to all patients only at the beginning of the procedure. The OAA/S scale was determined every 2 min, and the BIS score was continuously assessed. Sedation was started with intravenous injection of 20 mg propofol and constantly titrated by either method in increments of repeated boluses (10 mg) of intravenous propofol to achieve either OAA/S sores of 2–4 in the control group or a BIS score of 70–85 in the BIS group.

Patient Monitoring and Sedation-Related Interventions
In both groups, monitoring included continuous electrocardiography, pulse oximetry and automated noninvasive blood pressure recordings every 5 min. In addition, $TcCO_2$ was measured with a cutaneous digital sensor (Sentec AG, Therwil, Switzerland), which was placed on the earlobe prior to the procedure.

During the procedure, all patients received supplemental nasal oxygen at 2–5 l/min. Significant hypoxemia, defined as SpO_2

<90%, was treated initially with jaw support. If it lasted more than few seconds, a nasal/oropharyngeal tube was inserted or supplemental oxygen was delivered via face mask (100% O_2 at 10 l/min). In case of hypercapnia (defined as $TcCO_2$ >55 mm Hg), Ambu mask ventilation [17] was used [18]. Hypotension (defined as systolic blood pressure <90 mm Hg) was treated with a 500-ml bolus of normal saline solution. If the patient remained hypotensive despite fluid challenge, 0.1 mg i.v. phenylephrine was administered.

Structured Brice Interview

To assess patients' awareness during the procedure, the structured Brice interview [18] was conducted following recovery and prior to discharge. Briefly, it consists of a set of 5 questions assessing the patients' level of consciousness during sedation and throughout the procedure and unpleasant memories that might have occurred. The interview was conducted by a research assistant who was unaware to which subgroup the patient was allocated prior to the procedure.

Study End Points

The primary end point was the incidence of sedative-related adverse events requiring intervention during the procedure, which were defined as: hypotension (systolic blood pressure <90 mm Hg), hypoxemia (O_2 saturation <90%) despite oxygen administration (2 l/min) by nasal cannula and hypercapnia (defined as $TcCO_2$ >55 mm Hg).

Secondary end points were the total dosage of propofol used in each study arm and the patient's level of awareness during the procedure assessed by Brice interview, which was conducted following recovery.

Statistical Analysis

The null hypothesis (H0) was defined as no difference in the mean dosage of propofol used between the two intervention groups. According to a previous report [8], the mean dosage of propofol used for moderate sedation during bronchoscopy was 135 ± 71 mg. Sample size determination (unpaired t test, power 0.80, two-sided type I error 0.05) was performed with an estimated difference of 45 mg propofol between the two intervention groups. The estimated difference between the groups was based on the wide variability in the dosage of propofol required for sedation during bronchoscopy, which ranged in the study by Clark et al. [8], for example, from 65 to 200 mg. Accordingly, at least 40 subjects were needed in each group for H0 rejection.

Statistical analyses were carried out by χ^2 test and Student's t test, as appropriate. The unpaired t test was used to compare data between the different groups, while the paired t test was utilized to compare data within the same group. $p < 0.05$ was considered statistically significant. Data were analyzed using SPSS software (v14.0).

Results

Of 96 patients assessed for eligibility, 81 patients were randomized to one of the two groups (9 patients refused to participate in the study and 6 patients did not meet in-

Table 1. Baseline clinical and procedural characteristics of the study patients

Parameters	BIS	Control
Patients, n	40	41
Male/female ratio	22/18	23/17
Age, years	62.5±12.3	61.5±12
Range	24–86	25–87
Procedure, n		
Bronchoalveolar lavage	38	40
Endobronchial biopsy	11	16
Transbronchial needle aspiration	3	4
Transbronchial biopsy	11	16
Mechanical debridement/dilatation	1	2
Bronchial brushing	3	5
Laser	4	2
Duration of the procedure, min	18	19
Baseline vital signs (before the procedure)		
$TcCO_2$, mm Hg	38.6±5.2	35.7±6.3
SpO_2, mm Hg	98±1.3	98±1.2
DBP, mm Hg	73.8±11.6	72.1±15.3
SBP, mm Hg	143.9±21.5	141.7±19
HR, b.p.m.	77.2±15.1	81.5±13.5

Age and baseline vital signs are shown as means ± SD. DBP = Diastolic blood pressure; SBP = systolic blood pressure; HR = heart rate. No significant difference was found between groups.

clusion criteria). Table 1 shows the background data and clinical characteristics of the two groups. There were no significant between-group differences in demographics and the type of the bronchoscopic procedure used, or in hemodynamic parameters, oxygen saturation and $TcCO_2$ at baseline.

The mean total dose of propofol administered was not significantly different between the groups: 167.3 mg (range 60–530) in the control group and 168.7 in the BIS group (range 40–520; $p > 0.05$; fig. 1).

The mean rate (total dose/duration of procedure) was not significantly different between groups: 13.5 (mean of 10 boluses) versus 12.7 mg/min (mean of 9 boluses), respectively ($p > 0.05$).

Table 2 presents vital signs monitored during FFB, and the incidence of sedation-related events that required interventions. For all measured parameters, we also calculated the difference between the measured values and the values recorded before the procedure.

Systolic blood pressure was significantly lower in both groups during FFB compared to values before sedation; however, there was no significant difference between groups with respect to the lowest blood pressure mea-

Table 2. Procedure-related vital sign parameters and sedation-related complications and management

Parameters	BIS (n = 40)	Control (n = 41)
TcCO$_2$, mm Hg		
Maximum	54.67±13.2*	48.5±11.3*
Mean	47.1±10.3	42.7±7.4
SpO$_2$, mm Hg		
Minimum	87.6±3.7	89.1±5.3
Mean	96.4±1.6	94.4±2.6
DBP, mm Hg	73±9.8	70.5±11.9
SBP, mm Hg	138.3±21.6*	129±27.2*
HR, b.p.m.	77.6±12.7	81.4±12.1
Oxygen supplementation, n (%)	27 (67.5)	33 (82.5)
Naso/oropharyngeal tube insertion, n (%)	8 (20)	10 (25)
Ambu ventilation, n (%)	2 (5)	2 (5)
Fluid administration, n (%)	7 (17.5)	6 (15)
Phenylephrine administration (%)	2 (5)	3 (7.5)

Means ± SD and numbers (%) are shown. * $p < 0.05$ vs. before the procedure. There was no significant difference between groups. DBP = Diastolic blood pressure; SBP = systolic blood pressure; HR = heart rate.
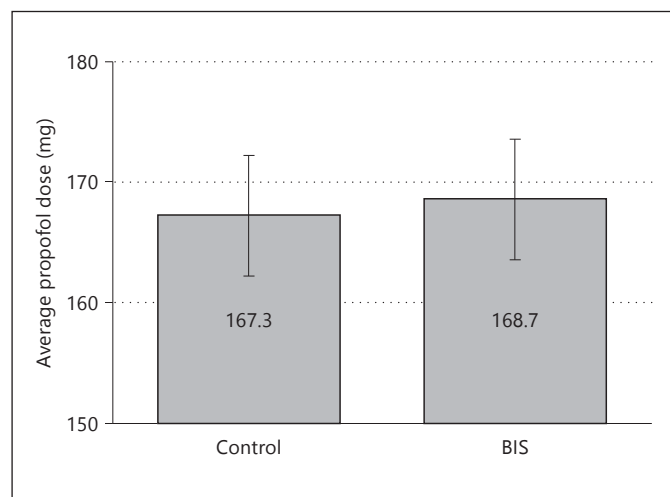

Fig. 1. Total average propofol dose used in the two study groups.

sured during the procedure. Significant hypotension requiring treatment by phenylephrine administration was noted in 3 (7.5%) patients in the control group and 2 patients (5%) in the BIS group ($p > 0.05$).

Mean O$_2$ saturation was similar in both study groups during FFB and was not significantly altered compared to baseline; a similar percentage of patients required O$_2$ supplementation by 100% O$_2$ mask due to hypoxemia: 33 patients (82.5%) in the control versus 27 patients (67.5%) in the BIS group ($p > 0.05$). The occurrence of hypercapnia requiring Ambu mask ventilation was similar in both groups (5% in the control and 5% in the BIS group).

None of the patients in either group complained of any pain or an unpleasant feeling during the procedure, and the structured Brice interview conducted following recovery but prior to discharge revealed no significant difference between groups with respect to patients' awareness during the procedure.

Discussion

The main finding of the current prospective randomized trial is that during short FFB procedures, the use of BIS to guide the depth of propofol sedation offers no additional benefit, neither with respect to patient's safety nor patient's satisfaction, compared to conventional monitoring.

In the modern era, FFB is usually performed under sedation [1–4] to achieve both patient and performer's comfort. To achieve the required level of sedation and ensure safety, the chosen pharmacological sedative should be administered by titration of small incremental doses to the desired clinical and physiological effect. Midazolam, with or without a short-acting opiate, was the traditional sedation agent for FFB due to its wide therapeutic window, its relatively short duration of action and the availability of the antidote flumazenil [4]. Midazolam is still considered by many authorities as the major drug of choice for sedation during FFB. Propofol is a lipophilic anesthetic agent with rapid distribution and elimination times, which has no cumulative effect after infusion. Its therapeutic spectrum is much narrower than that of midazolam, so careful monitoring is much more demanding to differentiate between moderate and deep sedation and general anesthesia [3]. Propofol has been evaluated in a variety of endoscopic procedures, including FFB, and has been shown to provide the same or superior sedation quality compared to midazolam with the advantage of better patient cooperation and shorter recovery time [6–10].

The conventional method to monitor the depth of sedation is usually performed using the 5-grade OAA/S scale. For moderate sedation, the depth of sedation should not exceed OAA/S score 3 [11].

EEG-guided sedation has been used by anesthesiologists to achieve optimal titration of sedatives. BIS monitoring is an EEG-based method that quantifies the depth of anesthesia by analyzing the EEG and uses a complex algorithm to generate an index score, providing an objective measurement of the level of consciousness in sedated patients [12, 13]. BIS monitoring has been shown to be useful and cost-effective in patients under general anesthesia. BIS may aid in monitoring the depth of sedation, but its routine introduction to sedation protocols during upper gastrointestinal procedures [14] and FFB is still debated. A recent prospective randomized trial failed to detect clinically significant advantages of BIS compared to conventional monitoring in patients undergoing upper gastrointestinal endoscopy under propofol sedation [14].

Two trials of moderate sedation during FFB using BIS monitoring concluded that BIS can be used safely by the non-anesthetist to titrate sedation with propofol [15, 16]. However, in both of these carefully designed trials, BIS was used only in the propofol arm whereas different sedative agents (midazolam and opiates) were used in the conventional monitoring arm. Hence, based on current available data, it is not clear whether the use of BIS monitoring is more cost-effective than the use of clinical judgment alone.

Since the costs of using BIS monitoring routinely in every FFB procedure are considerable (the currently listed price for the A-2000 BIS monitor is 11,000–15,000 USD and single-use BIS Quatro Sensors cost 15–40 USD), a clear clinical advantage of this method should be demonstrated.

In the current report, BIS monitoring did not result in a significant change in the dose of propofol used. In addition, no significant differences were noted with respect to various physiological parameters. Most importantly, BIS monitoring did not lead to a significant change in sedation-related side effects mandating interventions during the procedure, such as hypotension, hypoxemia and hypercapnia.

The first limitation of the current report is that only propofol was used as a sedative agent. Since midazolam is commonly used in many bronchoscopy suites, additional prospective randomized trials in which midazolam is used as a sedative agent with BIS monitoring versus conventional monitoring are necessary.

A major limitation of the current study is that most of the procedures were relatively simple and the majority did not include complex bronchoscopic interventions such as stent placement, hence our conclusions cannot be easily applied to the entire spectrum of bronchoscopic procedures. However, according to our current report, BIS monitoring during propofol sedation in procedures with a relatively short duration does not result in a safer and more desirable level of sedation, hence its routine use should not be considered. On the other hand, BIS monitoring may be useful in a subset of high-risk patients who are particularly prone to be over- or undersedated while monitored by clinical judgment alone, such as the elderly. BIS may be considered in lengthy procedures in which monitoring of sedation depth becomes a complicated issue, such as stent placement and other airway interventions of long duration.

Financial Disclosure and Conflict of Interest

There is no conflict of interest.

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