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Comparative Effects of Dexmedetomidine and Midazolam on Dreaming of Patients Undergoing Flexible Bronchoscopy During General Anesthesia

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The aim of this study was to compare the effects of dexmedetomidine versus midazolam on the dreaming of patients undergoing flexible bronchoscopy during general anesthesia.

Material/Methods: Patients undergoing flexible bronchoscopy under general anesthesia were randomly divided into a dexmedetomidine group (Group D, *n*=40) and a midazolam group (Group M, *n*=40). In group D, patients received 0.5 μg/kg dexmedetomidine and in group M patients received 0.05 mg/kg midazolam intravenously 10 min prior to induction. After bronchoscopy and recovery, a modified Brice questionnaire was used to immediately evaluate the incidence of dreaming of patients. Dreamers were required to complete a 5-point Likert scale survey regarding the contents of their dreams (emotion, voice and movement, memorability) if dreaming was reported. Ramsay Sedation Scale score (Ramsay score) and Visual Analogue Scale (VAS) score were assessed and recorded.

Results: Patients in group D had higher Ramsay scores and VAS scores (2.9±0.6 and 79.4±4.0, respectively) than group M (2.4±0.7 and 75.0±6.0, respectively), with a statistically significant difference ($P<0.05$) between groups. The incidence and memorability of dreaming were significantly lower in group D (17.5%) than group M (37.5%, $P<0.05$), whereas no significant difference was found in emotion, voice, and movement scores of dreaming.

Conclusions: Compared to midazolam, pre-injection of dexmedetomidine before induction significantly decreased the incidence of dreaming in patients undergoing flexible bronchoscopy during general anesthesia, without producing undesirable effects on the content of dreams (most of them were pleasant), produces a more efficacious sedation effect during the recovery period and improves the comfort level and satisfaction of patients.

Keywords: Anesthesia, General • Bronchoscopy • Dexmedetomidine • Dreams • Midazolam

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Background

Flexible bronchoscopy, the most valuable method for direct examination of airway, is commonly performed by physicians [1]. The application of bronchoscopy in patients is limited by the strong airway stimulation and psychological fear of patients. To improve these, the method of general anesthesia with laryngeal mask airway (LMA)-assisted ventilation is recently developed, which retains spontaneous breathing. This technique is advantageous in painless flexible bronchoscopy due to its safety, effectiveness, and ease of use [2]. Dreaming is a subjective experience which is produced both physically and psychologically during physical sleeping [3]. Although there are essential differences between anesthesia and sleeping, dreaming during anesthesia is common and is considered to be a different experience from anesthesia induction to awakening (except for intraoperative awareness). Dreams can be produced not only during long-duration surgery under general anesthesia, but also in brief surgeries, which are associated with a higher incidence rate of dreaming [4,5]. In addition, recent research has suggested that dreaming during general anesthesia has no effect on satisfaction of patients with the procedure. Dreaming under anesthesia, which is distinct from intraoperative awareness, is considered as a high-risk factor for awareness [6]. Light anesthesia is a major cause of dreaming and intraoperative awareness. Midazolam is a short-acting benzodiazepine hypnotic-sedative drug that can enhance the inhibition and blocking of cortical and limbic arousal by stimulating the inhibitory transmitter γ-aminobutyric acid (GABA) receptor in ascending reticular activating system. Consequently, midazolam produces favorable sedative and anterograde amnesia effects. Accumulating studies have shown that midazolam is one of the most widely used sedatives during bronchoscopy due to its anxiolytic and amnesic properties, as well as favorable pharmacokinetic characteristics such as rapid-onset and short-lasting inhibitory effects on the central nervous system. Moreover, it can be rapidly counteracted by flumazenil, a competitive antagonist for the benzodiazepine receptors, which enables rapid awakening and recovery of patients undergoing flexible bronchoscopy [7]. Dexmedetomidine is a new type of highly selective adrenoceptor agonist with sedative, amnestic, sympatholytic, and analgesic properties, which has been demonstrated to be effective for painless flexible bronchoscopy [8]. To date, no comparative studies have reported the effects of these 2 drugs on dreaming of patients undergoing flexible bronchoscopy during general anesthesia. The present study compared the effects of dexmedetomidine and midazolam on dreaming of patients undergoing flexible bronchoscopy during general anesthesia and assessed the incidence and characteristics of dreams, as well as the degree of sedation. Our results may provide a reference for satisfactory medical treatment using similar procedures in the future.

Material and Methods

Patients

This study was approved by the Institutional Review Board of the Hefei Affiliated Hospital of Anhui Medical University (IRB-approved registration number 20190711). Written informed consent from each patient was obtained before the study. A total of 80 patients posted from American Society of Anesthesiologists Grades I and II with flexible bronchoscopy under general anesthesia between March 2019 and June 2020 were reviewed, including 43 males and 37 females, aged 37~71 years old, and weighing of 47~84 kg. Inclusion criteria were: (1) undergoing flexible bronchoscopy under general anesthesia; (2) without language, mental, or comprehension impairment, and can communicate normally; (3) without history of neuropsychiatric disorders, drug dependence, and alcohol abuse; (4) without serious cardiovascular and cerebrovascular diseases, or major organ dysfunction preoperatively; (5) aged 18 to 75 years old; (6) sign the informed consent form. Exclusion criteria were: (1) history of known allergy to dexmedetomidine or midazolam; (2) language, mental, or comprehension impairment and inability to communicate normally; (3) history of neuropsychiatric disorders, drug dependence, or alcohol abuse; (4) serious cardiovascular and cerebrovascular diseases, or major organ dysfunction preoperatively; (5) older than 75 years old or younger than 18 years old; (6) participating in other clinical trials. All patients were randomly divided into either the dexmedetomidine group (Group D, n=40) or the midazolam group (Group M, n=40). Randomization was conducted using a random-permuted block randomization algorithm. The randomization sequence was kept in sealed envelopes. On the day of surgery, the investigator opened the envelope and prepared the study drug according to the allocated group and delivered it to the operating room wrapped with opaque paper. The result of the group allocation was not opened until the time of data analysis. In all cases, anesthesia was conducted by the same anesthesiologist and outcome assessments were carried out by another anesthesiologist, and both were blinded to the group allocation. There was no statistically significant difference in height, weight, age, procedure time, or other general characteristics between these 2 groups (P>0.05).

Methods

All patients were instructed not to eat for 8 hours or to drink for 4 hours prior to procedures and no preoperative drugs were administered. Routine monitoring devices were set up to monitor electrocardiogram, heart rate (HR), noninvasive blood pressure (BP), oxygen saturation (SpO_2), respiratory rate (RR), partial pressure of end-tidal carbon dioxide ($PetCO_2$), and bispectral (BIS) index of patients. O_2 at 2 L/min was applied through a nasal catheter and intravenous access was opened. All patients

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were atomized to inhale 5 ml 1% lidocaine before procedures. In group D, patients received 0.5 μg/kg dexmedetomidine and in group M patients received 0.05 mg/kg midazolam intravenously over a 10-min period before general anesthesia induction. Intravenous injection of fentanyl (1 μg/kg) and propofol (2.5 mg/kg) were given during induction. After emergence of consciousness, an i-gel laryngeal mask airway (manufactured by Intersurgical UK) was intubated. Vital signs, RR, and tidal volume were observed closely. In the case of weak breath, SpO_2 decrease, VT decrease, RR decrease, or apnea, the oxygen inhalation flow rate was increased, the ventilation mode of anesthesia machine was adjusted to synchronous intermittent instruction ventilation (SIMV) and intermittent positive pressure ventilation (IPPV), and VT, RR, and other parameters were modified accordingly. As the condition of patients stabilized, a fully lubricated bronchoscope was inserted into the glottis via swivel connector, which was connected to the i-gel and anesthesia equipment. Subsequently the procedure started and propofol was continuously infused at the rate of 5~7 mg/kg/h. Subsequently, 2% lidocaine solution 1 ml was applied via the suction channel of a flexible bronchoscope to avoid severe airway response during the procedure. The procedure was suspended if SpO_2 dropped below 90%. Patients were transferred to the recovery room after bronchoscopy. I-gel was extubated after the recovery of patient orientation to time and place.

Observation Indicators

General Data

We collected data on demographic characteristics (sex, age, weight, height, history of smoking) and usual condition of dreaming (0=never; 1=once a month; 2=once a week; 3=almost every day).

Intraoperative Data

We collected data on drug dose (propofol), duration of anesthesia (time between the induction and the end of anesthesia), duration of operation (time between the beginning and the end of anesthesia), and i-gel extubation time (time between withdrawal of drugs at the end of operation and i-gel extubation). The index of BIS at the time of entry (T_0), after induction and at the beginning of surgery (T_1), immediately after surgery (T_2), and i-gel extubation (T_3) were recorded.

Postoperative Data

The key points of evaluation were: Orientation recovery time (time between withdrawal of drugs and orientation of patients to time, place, and person) and Ramsay score during orientation recovery (Ramsay sedation scale: 1=patient anxious, agitated or restless or both; 2=patient cooperative, oriented, tranquil, and alert; 3=patient responds to commands; 4=asleep, but with brisk response to light glabellar tap or loud auditory stimulus; 5=asleep, sluggish response to light glabellar tap or loud auditory stimulus; 6=asleep, shows no response to light glabellar tap or loud auditory stimulus) [9]. The comfort level of patients after surgery was assessed by VAS score (0=highest possible dissatisfaction, 100=highest possible satisfaction).

Time and Method of Dreaming Investigation

After emergence from sedation and orientation recovery, a modified Brice questionnaire was immediately used to evaluate the incidence of dreaming. Patients who reported dreaming were required to complete a 5-point Likert scale survey regarding the contents of their dreams.

Modified Brice questionnaire [10]:

1) What is the last thing you remember before going to sleep?
2) What is the first thing you remember after waking up?
3) Do you remember anything between going to sleep and waking up?
4) Did you dream during your procedure?

The 5-Point Likert Scale [11]:

1) Dream is pleasant or unpleasant: 1=very unpleasant; 2=unpleasant; 3=moderately pleasant; 4=pleasant; 5=very pleasant;
2) Memorability of dream: 1=not remember at all; 2=remember a little; 3=moderate; 4=remember mostly; 5=remember completely;
3) Talking in dream: 1=no talking at all; 2=a little talking; 3=moderate talking; 4=a great deal of talking; 5=constant talking;
4) Action in dream: 1=no action; 2=a little action; 3=moderate action; 4=a great deal of action; 5=constant action.

Statistical Analysis

According to previous research data [7], using PASS 15.0 software (NCSS, LLC, Kaysville, USA), and based on 80% power and a 5% margin of error, the total sample size needed was calculated to be 79 (39 in group D and 40 in group M). A total of 80 participants were finally included, with 40 in each group.

Statistical analysis of the data collected was performed using SPSS software package (version 24.0; IBM Corporation, Armonk, NY). The independent-samples *t* test was used for inter-group comparison of normally distributed measurement data, measurement data with skewed distribution were expressed as median (interquartile range) [M(Q)], and the Mann-Whitney U test was used for inter-group comparison. The chi-square test was used for comparison of enumeration data. $P<0.05$ was considered as statistically significant.

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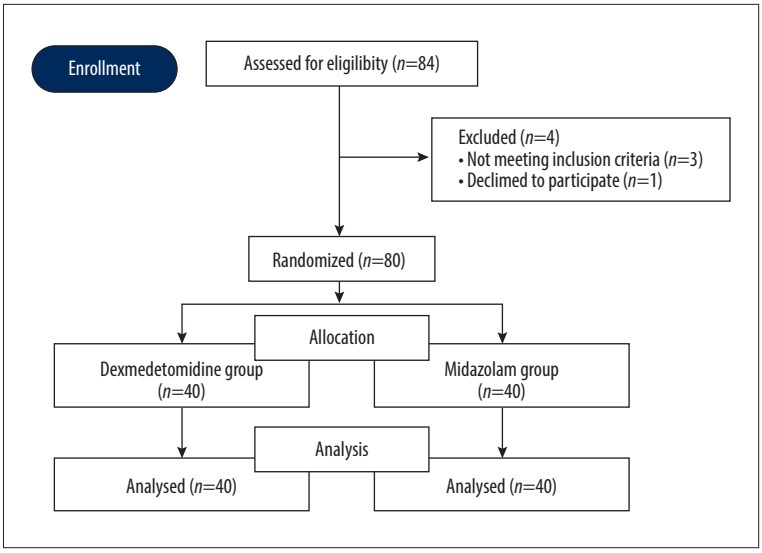

Figure 1. Flowchart based on Consolidated Standards of Reporting Trials (CONSORT) statement.

Table 1. Comparison of demographic information, clinical data of patients in the 2 groups (*n*=40, both).

Variables	Group D	Group M	*P*
Age (yr)	54.5±8.7	55.6±7.3	0.562
Weight (kg)	66.1±10.6	63.7±9.6	0.288
Height (cm)	166.5±7.4	165.4±8.8	0.553
Males/Females	22/18	21/19	0.823
History of smoking	17 (42.5%)	15 (37.5%)	0.648
Propofol dose (mg)	270.5±24.2	262.0±28.3	0.156
Duration of anesthesia (min)	22.9±3.9	23.6±3.2	0.390
Duration of operation (min)	19.9±3.8	20.6±3.4	0.399
i-Gel extubation time (min)	5.9±1.8	6.5±1.4	0.100
Orientation recovery time (min)	8.6±2.3	9.3±1.7	0.166
Usual condition of dreaming	N/A	N/A	N/A
0	2 (5.0%)	1 (2.5%)	0.556
1	5 (12.5%)	5 (12.5%)	1.000
2	27 (67.5%)	30 (75.0%)	0.458
3	6 (15.0%)	4 (10.0%)	0.499

Results

We included 84 patients in this study. One patient refused to participate and three patients did not meet inclusion criteria. The remaining 80 patients completed the study. The flowchart is summarized in **Figure 1**. **Table 1** summarized the comparison between group D and M. There were no significant differences between 2 groups in sex, age, weight, height, history of smoking, drug dose, duration of operation and anesthesia, i-gel extubation time, and usual condition of dreaming.

There was also no significant difference between the 2 groups in the BIS index at different times (**Table 2**).

Interestingly, compared to group M, patients in group D had higher Ramsay scores and VAS scores, and the differences were statistically significant ($P<0.05$) (**Table 3**).

Dreaming frequency was statistically different ($P<0.05$) between groups (**Table 4**), with group D reporting more dreaming (17.5%) than group M (37.5%).

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Table 2. Comparison of BIS index of patients in the 2 groups (*n*=40 each).

Group	T_0	T_1	T_2	T_3
Group D	95.6±1.5	55.0±1.8	65.9±2.1	88.9±2.5
Group M	95.4±1.8	55.4±1.9	65.3±2.0	88.6±3.0
P	0.557	0.299	0.230	0.605

Table 3. Ramsay score and VAS score of patients in the 2 groups (*n*=40 each).

Items	Group D	Group M	*P*
Ramsay score	2.9±0.6**	2.4±0.7	<0.01
VAS score (mm)	79.4±4.0**	75.0±6.0	<0.01

Compared with group M, ** P<0.01.

Table 4. Incidence of dreaming of patients in the 2 groups (*n*=40 each).

Items	Group D	Group M	*P*
Case of dream	7 (17.5%)*	15 (37.5)	0.043

Compared with group M, * P<0.05.

Table 5. Comparison of Likert score of the 2 groups (*M*(*Q*)).

Group	n	Emotion	Memorability	Voice	Motion
Group M	15	4 (1)	3 (1)	2 (1)	2 (1)
Group D	7	4 (1)	2 (1)*	2 (0)	2 (1)
P	N/A	0.783	0.011	0.783	0.581

Compared with group M, * P<0.05.

In the final analysis, the characteristics of recallable dreams were further examined and summarized in **Table 5**. Most of the dreams recalled by patients in both groups were pleasant. Compared to group M, the memorability of dreams in group D was lower (*P*<0.05), while no significant difference was found in terms of emotion, voice, and movement scores of dreams. During the bronchoscopy procedure and recovery period, there was no significant difference in blood pressure, blood oxygen saturation, or heart rate between group M and group D (*P*>0.05).

Discussion

Although bronchoscopy is a minimally invasive procedure, it inevitably introduces strong irritants to patients, which leads to severe coughing and strong fluctuations in hemodynamics during the procedure. In addition to psychological fear, it is potentially life-threatening to patients. To address these problems, painless flexible bronchoscopy has been developed and widely applied. In this study, after anesthesia induction i-gel was intubated, which can guarantee ventilation, and then the operation was started. Notably, the i-gel airway is a novel supraglottic airway device with a unique non-inflatable cuff made of thermoplastic elastomer. The gel-like cuff accurately mirrors perilaryngeal anatomy to create a perfect fit [12]. Overall, the methods were used to minimize the risk during the procedure and ensure patients' safety.

Dreaming during anesthesia is defined as any experiences and thoughts that occur between anesthesia induction and the time of awakening. During physiological sleep, most dreams that people can recall after awakening occur during the stage of rapid eye movement sleep. The occurrence of dream during anesthesia is affected by several factors, such as race, sex, depth of anesthesia, length of anesthesia time, and anesthetic drugs. In this study, the comparison between dexmedetomidine and midazolam was examined, with no significant differences in sex, age, weight, height, history of smoking, usual condition of dreaming, dosage of drugs, operation and anesthesia time, i-gel extubation time, and orientation recovery time of patients between the 2 groups. The BIS index was maintained at the same level during anesthesia. Overall, the indicators mentioned above had no effect on the results. The Brice questionnaire and 5-point Likert scale are widely used in clinically evaluating dreams, and these were used in the present study. Our results demonstrated that the frequency of dreaming in group D (17.5%) was lower than that in group M (37.5%), which suggests that dexmedetomidine reduces the incidence of dreaming during general anesthesia when compared to midazolam. Dexmedetomidine is an α_2 adrenergic agonist that exhibits various advantages over traditional benzodiazepines drugs,

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including weak respiratory inhibition and weak mucosal stimulation. α_2 adrenergic agonists are abundant in the locus ceruleus and nucleus pulposus in the brainstem and are closely related to anxiety, sleep-wake, and withdrawal of antianxiety drugs [13]. The locus ceruleus and dorsal raphe nuclei play critical roles in regulation of sleep. Upon sedation by dexmedetomidine, the locus ceruleus is inhibited, and ventrolateral preoptic area activity is elevated, which is similar to the stage of non-rapid eye movement [14].

Previous studied have revealed that light anesthesia may be one of the contributing factors for occurrence of dreaming [5]. In the present study, Ramsay scores in group D were higher than that of group M when orientation was restored, indicating that the level of sedation in group D was deeper; therefore, the incidence of dreaming was lower in group M. More importantly, most of the recallable dreams reported in this study were pleasant. Compared to group M, group D had less voice and motion in dreams, as well as a significantly lower memorability of dreams. These phenomena are potentially related to the depth of sedation (Ramsay score), as supported by previous studies [15]. The satisfaction of patients in group D was notably higher than in group M, which could be attributed to the effects of dexmedetomidine on sedation, analgesia, and antianxiety and decrease of airway reactivity [16]. Moreover, we found that the vital signs (eg, blood pressure, heart rate, and blood oxygen saturation) of the 2 groups were at the ideal levels, and there was no statistically significant difference during the bronchoscopy procedure and recovery period, indicating the safety of these 2 drugs.

However, there are several limitations in the study. First, no study was performed on the long-term effects after bronchoscopy. Moreover, variation in occurrence and contents of dreams during anesthesia was found in patients with different cultural backgrounds, religious beliefs, and living environments. In addition, the description and memorability of dreams by patients were subjective. During the interview, recall and narration from dreamers might not necessarily accurately represent their actual dreams. In addition, limitations also exist in the methods used. To address these issues, in future studies we will compare the results of groups of patients with different sex ratios and levels of education. Furthermore, we will improve the objectivity of our results by use of more advanced equipment, such as electroencephalogram and auditory evoked potential equipment. Long-term follow-up studies after surgery are needed to continue the investigation of the condition and content of dreaming in patients undergoing flexible bronchoscopy. Undoubtedly, the present study and future research on the factors influencing dreaming under anesthesia will provide valuable insights into this phenomenon.

Conclusions

In summary, compared to midazolam, pre-injection of dexmedetomidine before anesthesia induction significantly decreased the incidence of dreaming in patients undergoing flexible bronchoscopy. Although they both produced no effect on the content of dreams (most of them were pleasant), dexmedetomidine decreased the incidence of agitation. Overall, it provides more effective sedation during recovery and improves patient comfort and satisfaction.

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