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The safety and efficacy of dexmedetomidine-remifentanil in children undergoing flexible bronchoscopy

A retrospective dose-finding trial

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Abstract

Flexible bronchoscopy is more and more used for diagnosis and management of various pulmonary diseases in pediatrics. As poor coordination of children, the procedure is usually performed under general anesthesia with spontaneous or controlled ventilation to increase children and bronchoscopists' safety and comfort. Previous studies have reported that dexmedetomidine (DEX) could be safely and effectively used for flexible bronchoscopy in both adulate and children. However, there is no trial to evaluate the dose-finding of safety and efficacy of dexmedetomidine-remifentanil (DEX-RF) in children undergoing flexible bronchoscopy.

The objective of this study is to evaluate the dose-finding of safety and efficacy of DEX-RF in children undergoing flexible bronchoscopy.

One hundred thirty-five children undergoing flexible bronchoscopy with DEX-RF were divided into 3 groups: Group DR1 (n = 47, DEX infusion at 0.5 μg·kg^{-1} for 10 minutes, then adjusted to 0.5–0.7 μg kg^{-1} h^{-1}; RF infusion at 0.5 μg kg^{-1} for 2 minutes, then adjusted to 0.05–0.2 μg kg^{-1} min^{-1}), Group DR2 (n = 43, DEX infusion at 1 μg kg^{-1} for 10 minutes, then adjusted to 0.5–0.7 μg kg^{-1} h^{-1}; RF infusion at 1 μg kg^{-1} for 2 minutes, then adjusted to 0.05–0.2 μg kg^{-1} min^{-1}), Group DR3 (n = 45, DEX infusion at 1.5 μg kg^{-1} for 10 minutes, then adjusted to 0.5–0.7 μg kg^{-1} h^{-1}; RF infusion at 1 μg kg^{-1} for 2 minutes, then adjusted to 0.05–0.2 μg kg^{-1} min^{-1}). Ramsay sedation scale of the 3 groups was maintained 3. Anesthesia onset time, total number of intraoperative children movements, hemodynamics (heart rate, arterial pressure, pulse oxygen saturation (SpO_2), respiratory rate), total cumulative dose of dexmedetomidine and remifentanil, the amount of midazolam and lidocaine, time to first dose of rescue midazolam and lidocaine, postoperative recovery time, adverse events, bronchoscopist satisfaction score were recorded.

Anesthesia onset time was significantly shorter in DR3 group (14.23 ± 5.45 vs 14.45 ± 5.12 vs 11.13 ± 4.51 minutes, respectively, of DR1, DR2, DR3, $P = 0.003$). Additionally, the perioperative hemodynamic profile was more stable in group DR3 than that in the other 2 groups. Total number of children movements during flexible bronchoscopy was higher in DR1 group than the other 2 groups (46.81% 22/47 vs 34.88% 15/43 vs 17.78% 8/45, respectively, of DR1, DR2, DR3, $P = 0.012$). Total doses of rescue midazolam and lidocaine were significantly higher in DR1 and DR2 groups than that of DR3 group ($P = 0.000$). The time to first dose of rescue midazolam and lidocaine was significantly longer in DR3 group than DR1 and DR2 groups ($P = 0.000$). Total cumulative dose of dexmedetomidine was more in DR2 and DR3 groups ($P = 0.000$), while the amount of remifentanil was more in DR1 and DR2 groups ($P = 0.000$). The time to recovery for discharge from the PACU was significantly shorter in DR1 group compared with the other 2 groups ($P = 0.000$). Results from bronchoscopist satisfaction score showed significantly higher in DR2 and DR3 groups than that of DR1 group ($P = 0.025$). There were significant differences among the 3 groups in terms of the overall incidence of hypertension, tachycardia, hypoxemia, and cough ($P < 0.05$).

Though it required longer recovery time, high dose of DEX-RF, which provided better stable hemodynamic profiles and bronchoscopist satisfaction score, less amount of rescue scheme, and children movements, could be safely and efficacy used in children undergoing flexible bronchoscopy.

Abbreviations: ASA = American Society of Anesthesiology, BMI = body mass index, DEX = dexmedetomidine, HR = heart rate, IQR = interquartile range, MAC = monitored anesthesia care, MAP = mean arterial pressure, PACU = postanesthesia care unit, RF = remifentanil, RR = respiratory rate, SpO_2 = pulse-oximetry, TEM = temperature.

Keywords: dexmedetomidine, flexible bronchoscopy, hemodynamic stability, paediatric, remifentanil

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1. Introduction

More and more bronchoscopic interventional procedures have been used since the flexible bronchoscopy was the first application in 1968.[1] Many of these procedures are performed under anesthesia for a higher success rate and more comfortable, especially for children who could not cooperate.[2,3] Providing appropriate degree of anesthesia to meet the procedural needs is a unique challenge for anesthesiologist, as both anesthesiologist and operator share the same airway.[4] Short acting opioids, newer drugs such as dexmedetomidine, supraglottic airways, and mechanical jet ventilators have facilitated the conduct of this procedure. Even so, with the increase of adverse events, most of the professional outfit are now opting for setting up a technical team with dedicated anesthesiologist.[5–7]

Though general anesthesia still remains the standard technique for complex procedures, conscious sedation compared with topical anesthesia has come up as the commonly used anesthetic technique for simple flexible bronchoscopy recently.[3,8] Ideal anesthesia requires sedative, hypnosis, analgesia, and muscle relaxation. Midazolam, propofol, etomidate, opioids, inhalational agents, or a combination of these drugs have been widely used during flexible bronchoscopy; however, each of these drugs has its limitations.[9–12] Midazolam, propofol, and etomidate have no analgesic property and sedative pharmacology variability of different patients may be responsible for respiratory depression. Opioids such as fentanyl, sufentanil, and remifentanil can provide excellent analgesia without enough sedation. There are unavoidable defects in the inhalational agents such as air pollution, though these agents exert a synergistic action with sedative and muscle-relaxing drugs. Combined with these drugs can result in severe respiratory depression, which is the most common complication and the reason for failure in flexible bronchoscopy.[13,14] For the foregoing reasons, the need for ideal mode of drug combinations that can be used safely and effectively during children's flexible bronchoscopy, meanwhile with limited adverse effects, is urgent.

Dexmedetomidine (DEX), a highly selective agonist of α 2 adrenergic receptor, has more favorable pharmacokinetic profile than clonidine.[15] Previous studies have reported that DEX alone or compared with midazolam, propofol, or opioids could be safely and effectively used for flexible bronchoscopy in both adult and children.[9,16,17] However, according to the independent search of MEDLINE, PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science for English language articles between 1990 and 2015 using dexmedetomidine, remifentaniland, paediatric, flexible bronchoscopy, and dose-finding, there have been no trials to report the dose-finding of DEX-RF in children undergoing flexible bronchoscopy. We conducted this retrospective trial to evaluate the dose-finding of safety and efficacy of DEX-RF in children undergoing flexible bronchoscopy.

2. Materials and methods

2.1. Patients

We obtained the Institutional Review Board of Liaocheng People's Hospital approval for this retrospective clinically dose-finding trial. Children undergoing flexible bronchoscopy between January 2015 and December 2015 with written informed consent of their parents were enrolled in this study if they met the following inclusion criteria: age between 5 and 10 years, ASA grades I to II. Exclusion criteria included congenital disease, second or third degree heart block, DEX and remifentanil allergy, asthma, neuropsychiatric diseases, operation time longer than 1 hour, pulse oxygen saturation <90% before flexible bronchoscopy, body mass index (BMI) >30 kg m^{-1} and those who refused to give informed consent.

Patients were divided into 3 groups: Group DR1 (n = 47, DEX infusion at 0.5 μg kg^{-1} for 10 minutes, then adjusted to 0.5–0.7 μg kg^{-1} h^{-1}; RF infusion at 0.5 μg kg^{-1} for 2 minutes, then adjusted to 0.05–0.2 μg kg^{-1} min^{-1}), Group DR2 (n = 43, DEX infusion at 1 μg kg^{-1} for 10 minutes, then adjusted to 0.5–0.7 μg kg^{-1} h^{-1}; RF infusion at 1 μg kg^{-1} for 2 minutes, then adjusted to 0.05–0.2 μg kg^{-1} min^{-1}), Group DR3 (n = 45, DEX infusion at 1.5 μg kg^{-1} for 10 minutes, then adjusted to 0.5–0.7 μg kg^{-1} h^{-1}; RF infusion at 1 μg kg^{-1} for 2 minutes, then adjusted to 0.05–0.2 μg kg^{-1} min^{-1}). Electronic chart and DoCare Clinic electronic anesthesia recording system data were utilized during this trial. All children and their parents were explained about the operative procedure. The flexible bronchoscopy was performed by the same bronchoscopist who was 10 years of residency.

According to ASA guideline, all children were fasted for 6 hours from solids and 2 hours from clear fluids before flexible bronchoscopy.[18] After baseline hemodynamic parameters were obtained, i.v. midazolam 0.03 mg kg^{-1} and atropine 0.01 mg kg^{-1} were given in the reception area, then children were transferred to the operating room.[19] ASA standard monitoring 5-lead electrocardiography, noninvasive arterial blood pressure, peripheral pulse-oximetry (SpO_2), respiratory rate (RR), and temperature (TEM) were continuously monitored using an automated system (Philips IntelliVue MP70). All children received oxygen supplementation at 3 L min^{-1} through a nasal cannula, then a 22-gauge intravenous catheter was placed in a peripheral vein. A forced-air warming device (EQUATOR Convective Warmer, EQ-5000) was used during the procedure to maintain normothermia.

2.2. Flexible bronchoscopy

After loading doses of DEX and RF infusion for 10 minutes, topical anesthesia was performed using 2 mL of 1% lidocaine spray in the oral cavity. On visualizing the vocal cords, trachea, and the right and left main bronchi, 3 mL of 1% lidocaine was delivered through the flexible bronchoscope channel to suppress the cough reflection. Once topicalization was completed and the Ramsay sedation score reached 3 (children exhibit subject responds to commands), flexible bronchoscope was performed. Whenever indications of insufficient sedation were observed during the procedure, a rescue bolus of midazolam 0.02 mg kg^{-1} was given repeatedly every 5 minutes to a maximum dose of 1.5 mg, or an additional 1 mL of 1% lidocaine was administered through the side hole of a flexible bronchoscope to a maximum dose of 10 mL. The amount of midazolam and lidocaine administered was recorded. If the patient did not reach the ideal status after the maximum dose of midazolam and lidocaine, propofol 1 mg kg^{-1} was provided. DEX and RF infusion were stopped until flexible bronchoscopy finished. All patients received tropisetron 0.1 mg kg^{-1} and were transferred to the postanesthesia care unit (PACU) after bronchoscopy.

On arrival at the PACU, hemodynamic data (HR, noninvasive blood pressure, RR, SpO_2, TEM) were monitored every 5 minutes for the first 20 minutes, then every 10 minutes for the rest of the time until children were discharged (the Aldrete Score ≧9).[20] Bronchoscopist satisfaction was assessed (1, extremely dissatisfied; 2, not satisfied but able to manage; 3, extremely satisfied; 4, extremely dissatisfied) 24 hours after flexible bronchoscopy.[21] All children were continuously moni-

tored by 5-lead electrocardiography, noninvasive arterial blood pressure, and peripheral pulse-oximetry (SpO_2) using an automated system (Philips IntelliVue MP70) for at least 12 hours after flexible bronchoscopy.

2.3. Adverse events

During the procedure, bradycardia and tachycardia were defined as 30% beyond the baseline of heart rate and treated by atropine 0.2 mg or esmolol 0.3 mg kg^{-1} iv respectively. Hypertension and hypotension were defined as 30% beyond the baseline of mean arterial blood pressure and treated by urapidil (10 mg) or ephedrine (6 mg). Hypoxemia was defined as SpO_2 was <90% for >30 seconds and treated with oxygen supplementation at 6 L min^{-1} or verbal and tactile stimulation, chin lifts, jaw thrusts, a face mask, and manual ventilation.

2.4. Outcome variables

The intraoperative hemodynamic data (HR, noninvasive blood pressure, RR, SpO_2, TEM) obtained from Phillips IntelVue monitor were recorded at the following time points: arrival at the operating room (T1), after bolus administration of drug (T2), at the initiation of flexible bronchoscopy (T3), 1 minute after initiation of bronchoscopy (T4), 5 minutes after initiation of bronchoscopy (T5), 10 minutes after initiation of bronchoscopy (T6), at the end of bronchoscopy (T7) and arrival (T8), 5 minutes (T9), 10 minutes (T10) at the PACU. Anesthesia onset time, total number of intraoperative children movements, total cumulative dose of dexmedetomidine and remifentanil, the amount of midazolam and lidocaine, time to first dose of rescue midazolam, postoperative recovery time (between withdrawal of flexible bronchoscope and the discharged from PACU), adverse events, bronchoscopist satisfaction score were recorded.

2.5. Statistical analysis

The Kolmogorov–Smirnov test was used to assess the distribution of variables. Homogeneity of variance was determined using Levene tests. Quantitative data was expressed as mean and standard deviation or median and interquartile range (IQR). Intergroup comparisons were performed using repeated-measures analysis of variance. The Bonferroni correction was used for post-hoc multiple comparisons. The nonparametric Kruskal–Wallis test was used for variables that were not normally distributed. Categorical data was expressed as frequency and percentage and analyzed using χ^2 tests or Fisher exact tests when appropriate. Probability (P) values <0.05 were considered statistically significant. Statistical analysis was performed with SPSS for Windows Version 18.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Baseline characteristics

Two hundred seven children undergoing flexible bronchoscopy were screened between January 2015 and December 2015 (Fig. 1). Seventy-two children were excluded because of not meeting the inclusion criteria: 6 children had congenital disease, 2 children had second degree heart block, 12 children had a history of asthma, 10 children had neuropsychiatric diseases, the operation time of 24 children was longer than 1 hour, pulse oxygen saturation of 8 children was <90% before flexible bronchoscopy, body mass index (BMI) of 6 children was >30 kg m^{-1} and parents of 4 children refused to give informed consent. At last, a total of 135 children were included in the primary analysis and were divided into 3 groups (47 children from DR1 group, 43 children from DR2 group, 45 children from DR3 group). Demographic and baseline clinical parameters were not significantly different among the 3 groups ($P > 0.05$, Table 1).

3.2. Intraoperative variables

Baseline hemodynamic was not statistically different among the 3 groups ($P > 0.05$, Fig. 2). Compared with DR1 group, both HR and MAP in DR2 and DR3 groups were significantly decreased from T2 to T10 ($P < 0.05$, Fig. 2). Compared with DR2 group, HR in DR3 group was significantly decreased from T3 to T7, while MAP was significantly decreased from T3 to T6 ($P < 0.05$, Fig. 2).

Comparing the 3 groups, we found that anesthesia onset time was significantly shorter in DR3 group (14.23 ± 5.45 vs 14.45 ± 5.12 vs 11.13 ± 4.51 minutes, respectively, of DR1, DR2, DR3, $P = 0.003$, Table 2). Total doses of rescue midazolam (1.22 ± 0.35 vs 1.15 ± 0.39 vs 0.78 ± 0.24 mg, respectively, of DR1, DR2, DR3, $P = 0.000$) and lidocaine (7.68 ± 2.35 vs 6.89 ± 2.01 vs 4.23 ± 1.25 mL, respectively, of DR1, DR2, DR3, $P = 0.000$) were significantly higher in DR1 and DR2 groups than that of DR3 group (Table 2, Fig. 3). The time to first dose of rescue midazolam (11.47 ± 3.23 vs 13.89 ± 3.32 vs 15.46 ± 3.54 min, respectively, of DR1, DR2, DR3, $P = 0.000$) and lidocaine (15.15 ± 3.74 vs 17.34 ± 4.58 vs 22.65 ± 3.32 min, respectively, of DR1, DR2, DR3, $P = 0.000$) was significantly longer in DR3 group than DR1 and DR2 groups (Table 2). Total cumulative dose of dexmedetomidine was more in DR2 and DR3 groups (35.45 ± 12.98 vs 50.92 ± 23.27 vs 65.24 ± 17.29 μg, respectively, of DR1, DR2, DR3, $P = 0.000$). Total cumulative dose of remifentanil was more in DR1 and DR2 groups (164.33 ± 35.84 vs 105.49 ± 34.11 vs 90.29 ± 22.50 μg, respectively, of DR1, DR2, DR3, $P = 0.000$).

Total number of children movements during flexible bronchoscopy was higher in DR1 group than the other 2 groups (46.81% 22/47 vs 34.88% 15/43 vs 17.78% 8/45, respectively, of DR1, DR2, DR3, $P = 0.012$, Table 2). Though most of the patient movements could be controlled with Dex and DR infusion adjustment and rescue drugs (midazolam), there were still 12 children from DR1 group, 6 children from DR2 group, and 2 children from DR1 group who need to use the alternative sedative (propofol) to complete the flexible bronchoscopy (Table 2).

There were significant differences among the 3 groups in terms of the overall incidence of hypertension, tachycardia, hypoxemia, and cough (Table 3). As a result, more children in DR1 and DR2 groups need urapidil (36.17% 17/47 vs 20.93% 9/43 vs 11.11% 5/45, respectively, of DR1, DR2, DR3, $P = 0.016$) and esmolol (38.30% 18/47 vs 23.26% 10/43 vs 13.33% 6/45, respectively, of DR1, DR2, DR3, $P = 0.024$) to maintain the hemodynamic stability (Table 4).

3.3. Postoperative variables

The time to recovery for discharge from the PACU (time to an Aldrete score ≧9) was significantly shorter in DR1 group compared with the other 2 groups (10.27 ± 5.21 vs 13.64 ± 5.59 vs 17.23 ± 7.66 minutes, respectively, of DR1, DR2, DR3, $P = 0.000$, Table 5). Results from bronchoscopist satisfaction score

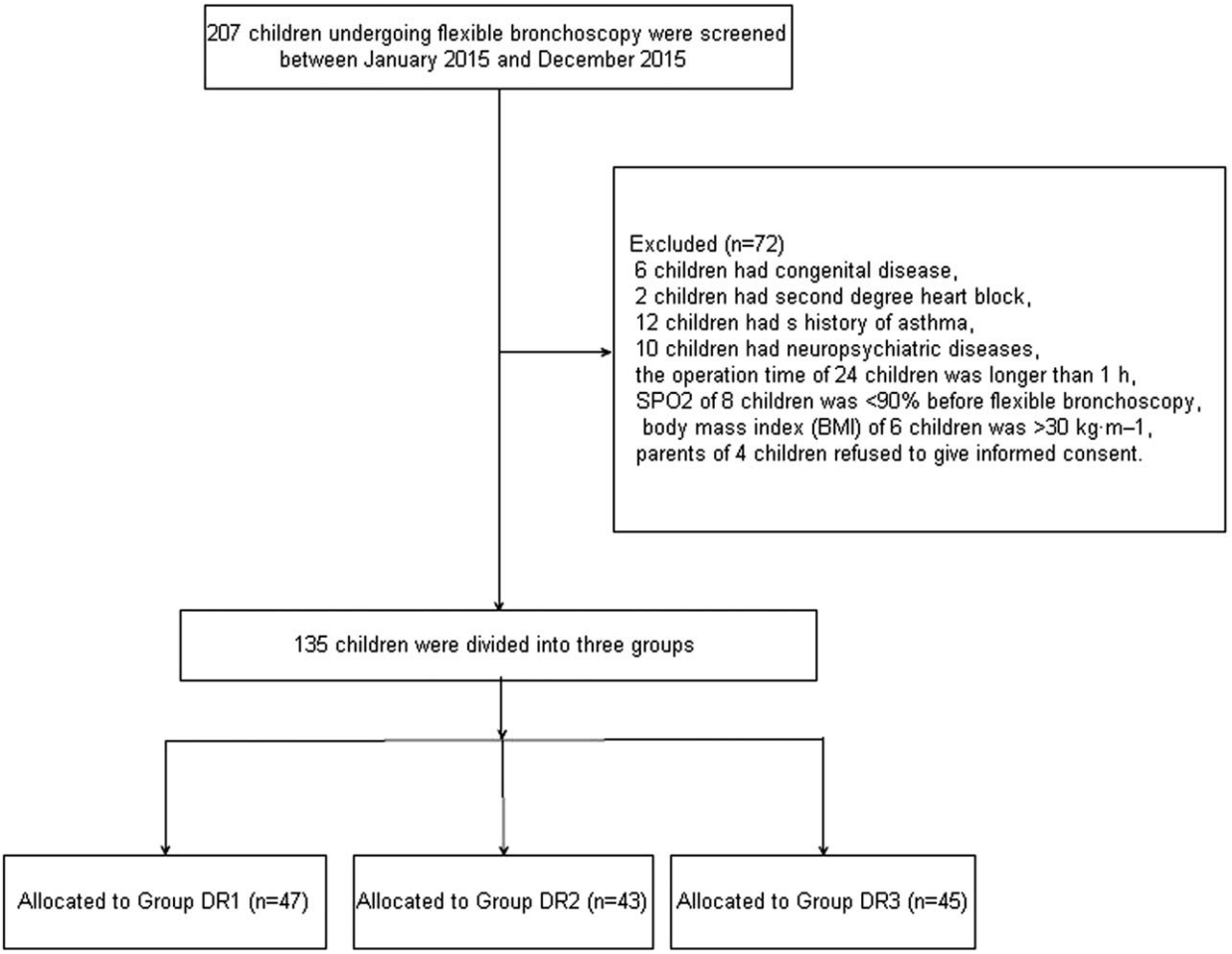

Figure 1. Patient enrollment flow diagram. This illustrates the flow of all patients screened and excluded.

showed significantly higher in DR2 and DR3 groups than that of DR1 group ($P=0.025$, Table 5).

4. Discussion

High dosage of DEX combined with RF (DEX infusion at 1.5 μg kg^{-1} for 10 minutes, then adjusted to 0.5–0.7 μg kg^{-1} h^{-1}; RF infusion at 1 μg kg^{-1} for 2 minutes, then adjusted to 0.05–0.2 μg kg^{-1} min^{-1}) could shorten the anesthesia onset time, decreased the number of intraoperative patient movements and the overall incidence of hypertension, tachycardia, hypoxemia, and cough, which may be the principal reasons of higher bronchoscopist satisfaction score in DR3 group. Additionally, the perioperative hemodynamic profile was more stable in group DR3 than that in

Table 1

Demographic and baseline clinical parameters in the 3 groups.

Variable	Group DR1 (n=47)	Group DR2 (n=43)	Group DR3 (n=45)	*P* values
Age, y	7.32±1.45	8.07±1.90	7.28±1.78	0.055
Body weight, kg	29.48±5.83	31.91±6.24	30.29±5.96	0.155
Sex (male/female)	27/20	25/18	30/15	0.607
BMI, kg m^{-2}	26.23±4.55	27.94±5.08	26.69±4.02	0.192
ASA (I/II)	28/19	27/16	25/20	0.787
Duration of anesthesia, min	40.23±11.76	43.15±12.03	39.74±10.54	0.324
Duration of bronchoscopy, min	27.34±8.89	31.21±9.23	28.47±9.02	0.120
Type of bronchoscopy, n (%)				
Inspection	25 (53.19%)	23 (53.49%)	25 (55.56%)	
Bronchoalveolar lavage	9 (19.15%)	10 (23.26%)	8 (17.78%)	0.985
Transbronchial biopsy	7 (14.89%)	6 (13.95%)	8 (17.78%)	
Others	6 (12.77%)	4 (9.30%)	4 (8.89%)	

Variables presented as mean±SD or number of patients n (%).
ASA=American Society of Anesthesiology, BMI=body mass index.

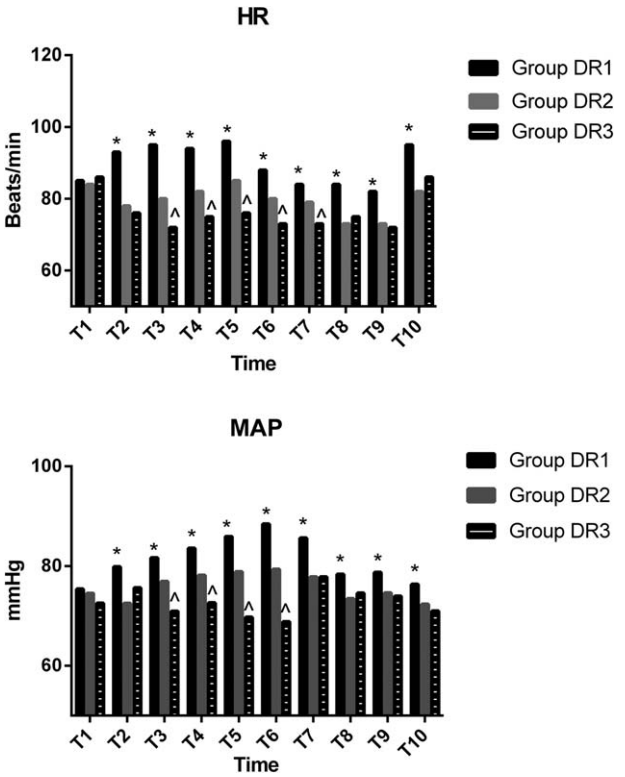

Figure 2. Hemodynamics were monitored in the 3 groups. Baseline hemodynamic were not statistically difference among the 3 groups ($P > 0.05$). Compared with DR1 group, both HR and MAP in DR2 and DR3 groups were significantly decreased from T2 to T10 ($P < 0.05$). Compared with DR2 group, HR in DR3 group was significantly decreased from T3 to T7, while MAP was significantly decreased from T3 to T6 ($P < 0.05$). T1, arrival at the operating room; T2, after bolus administration of drug; T3, at the initiation of flexible bronchoscopy; T4, 1 min after initiation of bronchoscopy; T5, 5 min after initiation of bronchoscopy; T6, 10 min after initiation of bronchoscopy; T7, at the end of bronchoscopy; T8, arrival at PACU; T9, 5 min after arriving at PACU; T10, 10 min after arriving at PACU. $^{*}P < 0.05$ versus Group DR2 and Group DR3, ^ $P < 0.05$ versus Group DR2.

the other 2 groups. Children in DR3 group need less dose of rescue midazolam and lidocaine to complete the flexible bronchoscopy. The time to first dose of rescue midazolam and lidocaine was also significantly longer in DR3 group. However, the time to recovery for discharge from the PACU was significantly longer in DR3 group.

Bronchoscopy is usually divided into rigid and flexible bronchoscopy according to the application of equipment. Rigid bronchoscopy is usually used for airway or esophageal foreign body removal in adults and children, while flexible bronchoscopy is usually used for the diagnosis and treatment of respiratory diseases by respiratory physicians and pediatrician.[22] Rigid bronchoscopy is usually manipulated under general anesthesia for its long operation time and stimulation. While flexible bronchoscopy can be done under topical anesthesia, monitored anesthesia care (MAC), or general anesthesia.[3] The orthodox prediction is that general anesthesia still remains the gold standard technique for most bronchoscopy, especially in the rigid bronchoscopy and complex procedures of flexible bronchoscopy. However, monitored anesthesia care, such as conscious sedation compared with topical anesthesia, has been recently used in many clinical fields, particularly in simple flexible bronchoscopy. It can not only provide excellent operating conditions for bronchoscopist but also overcome some shortcoming of both GA (e.g., prolonged emergence and hospitalization time) and topical anesthesia (e.g., hemodynamics instability).[23,24]

Table 2

Comparison of intraoperative variables in the 3 groups.

Variable	Group DR1 (n = 47)	Group DR2 (n = 43)	Group DR3 (n = 45)	*P* values
Anesthesia onset time, min	14.23 ± 5.45	14.45 ± 5.12	11.13 ± 4.51*,†	0.003
Time to first dose of rescue midazolam, min	11.47 ± 3.23	13.89 ± 3.32*	15.46 ± 3.54*,†	0.000
Time to first dose of rescue lidocaine, min	15.15 ± 3.74	17.34 ± 4.58*	22.65 ± 3.32*,†	0.000
Total dose of rescue midazolam, mg	1.22 ± 0.35	1.15 ± 0.39	0.78 ± 0.24*,†	0.000
Total dose of rescue lidocaine, mL	7.68 ± 2.35	6.89 ± 2.01	4.23 ± 1.25*,†	0.000
Total dose of dexmedetomidine, μg	35.45 ± 12.98	50.92 ± 23.27*	65.24 ± 17.29*,†	0.000
Total dose of remifentanil, μg	164.33 ± 35.84	105.49 ± 34.11*	90.29 ± 22.50*,†	0.000
Total patient movements, n, %	22 (46.81%)	15 (34.88%)*	8 (17.78%)*,†	0.012
converted to propofol, n, %	12 (25.53%)	6 (13.95%)*	2 (4.65%)*,†	0.017

Variables presented as mean ± SD or number of patients n (%).
* $P < 0.05$ vs Group DR1.
† $P < 0.05$ vs Group DR2.

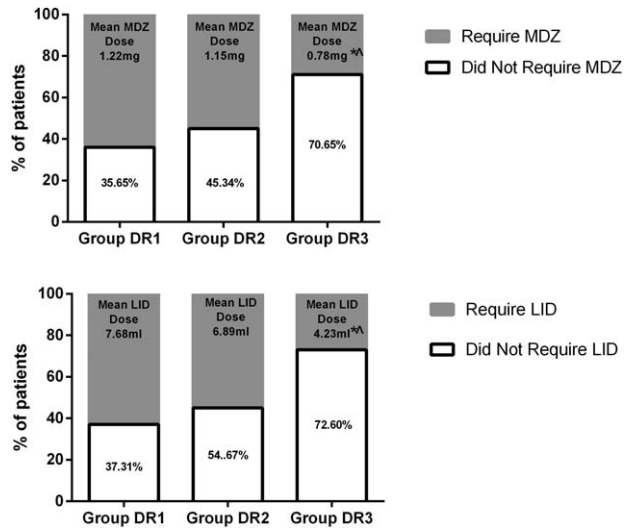

Figure 3. Percentage of patients who require rescue midazolam or lidocaine and mean midazolam or lidocaine dosage used during the study. $^{*}P<0.05$ versus Group DR2 and Group DR3, ^ $P<0.05$ versus Group DR2.

Alleviation of perioperative stress and improved satisfaction of patients, providing sedative, hypnosis, analgesia, and muscle relaxation condition for bronchoscopist without respiratory depression are primary goals for the anesthesiologist.[3] Benzodiazepines are one of the most commonly used sedatives during bronchoscopy. They play the role of sedative, hypnotic, anxiolytic, anticonvulsant, and muscle relaxing effects through gamma amino butyric acid receptor. Because of short elimination half-life and faster onset of action, midazolam is the first choice for such drugs. However, this drug may depress the ventilatory drive and finally cause apnoea as its sedative pharmacology variability of different patients, especially in those with comorbidities and taking other respiratory depressant drugs at the same time.[25,26] As a short-acting and rapid recovery anesthetic agent, propofol has been widely used in many clinical fields such as gastrointestinal endoscopy, thyroplasty, bronchoscopy, interventional or radiological procedures, and awake bronchoscopy intubation for its hypnotic effect. However, because of the narrow therapeutic index between moderate sedation and respiratory depression, propofol is now strongly recommended for use only by anesthesiologists with close monitoring.[27,28] Ketamine has been more and more used in the children's flexible bronchoscopy for its sympatholytic and analgesic effects as well as being a potent bronchodilator, but it has the deficiency of increasing salivation and secretions and cannot attenuate the upper airway reflexes.[29,30] Though opioids are frequently used during bronchoscopy for analgesic property, their sedative effect is weak to complete the procedure. It may lead to bradycardia, hypotension, and hyoxemia when in high doses or combined use of other sedative drugs.[14]

The scheme, combination of 2 or more agents, has been the usual solution adopted by bronchoscopist and anesthesiologist recently.[3,14] As a μ opioid receptor, remifentanil has short half-life and its analgesic potency was similar to fentanyl. Though previous studies have reported remifentanil in combination with propofol can be used for children's flexible bronchoscopy, it usually needs to take actions to inhibit patient movements and prevent hypoxia during the procedure.[11] DEX, a new selective alpha 2-agonist, has sedative, anxiolysis, and analgesia effects. Above all else, it has the advantage of causing mild respiratory depression even at higher doses. Previous studies have reported that DEX can both decrease the incidence of desaturation and reduce the secretions.[31,32]

It is generally recommended that DEX infusion of 1 μg kg^{-1} bolus for 10 minutes, and then infusion at a rate of 0.2 to 0.7 μg kg^{-1} h^{-1} for maintenance, RF infusion of 1 μg kg^{-1} bolus for 10 minutes, then followed by infusion at a rate of 0.2–0.7 μg kg^{-1} h^{-1}

Table 3

Adverse events of patients in the 3 groups.

Variable	Group DR1 (n = 47)	Group DR2 (n = 43)	Group DR3 (n = 45)	*P* values
Tachycardia	22 (46.81%)	15 (34.88%)*	10 (22.22%)*,†	0.045
Hypertension	24 (51.06%)	14 (32.56%)*	9 (20.00%)*,†	0.007
Bradycardia	8 (17.02%)	9 (20.93%)	7 (15.56%)	0.816
Hypotension	5 (10.64%)	6 (13.95%)	5 (11.11%)	0.893
Nausea	12 (25.53%)	10 (23.26%)	9 (20.00%)	0.816
Vomiting	2 (4.26%)	1 (2.33%)	2 (4.44%)	1.000
Cough	25 (53.19%)	18 (41.86%)*	12 (26.67%)*,†	0.033
Hypoxemia	18 (38.30%)	7 (16.28%)*	6 (13.33%)*,†	0.008

Variables presented as number of patients n (%).
* $P<0.05$ vs Group DR1.
† $P<0.05$ vs Group DR2.

Table 4

The vascular active drugs of 3 groups during bronchoscopy.

Variable	Group DR1 (n = 47)	Group DR2 (n = 43)	Group DR3 (n = 45)	*P* values
Urapidil	17 (36.17%)	9 (20.93%)*	5 (11.11%)*,†	0.016
Esmolol	18 (38.30%)	10 (23.26%)*	6 (13.33%)*,†	0.024
Ephedrine	2 (4.26%)	3 (6.98%)	3 (6.67%)	0.817
Atropine	4 (8.51%)	3 (6.98%)	5 (11.11%)	0.868

Variables presented as number of patients n (%).
* $P<0.05$ vs Group DR1.
† $P<0.05$ vs Group DR2.

Table 5

Comparison of postoperative variables in the 3 groups.

Variable	Group DR1 (n = 47)	Group DR2 (n = 43)	Group DR3 (n = 45)	*P* values
Recovery time, min	10.27 ± 5.21	13.64 ± 5.59*	17.23 ± 7.66*,†	0.000
Bronchoscopist satisfaction score	2.50 (1.25–2.75)	3.00 (2.25–3.75)*	3.75 (3.00–4.00)*,†	0.025

Variables presented as mean ± SD or median (interquartile range).

* $P < 0.05$ vs Group DR1.

† $P < 0.05$ vs Group DR2.

for maintenance. However, the pharmacokinetic age-related difference of DEX may cause children to need larger initial doses of DEX than adults to reach similar steady-state plasma levels as DEX has a larger apparent volume of distribution of children, while the maintenance doses are similar.[33,34] Owing to the reasons above, we adopt DEX infusion at 0.5 to 1.5 μg kg^{-1} for 10 minutes, then adjust to 0.5–0.7 μg kg^{-1} h^{-1}; RF infusion at 0.5–1 μg kg^{-1} for 2 minutes, then adjust to 0.05–0.2 μg kg^{-1} min^{-1} at this trial. Nonautonomous movement of children is one of the most common reasons of failure for flexible bronchoscopy. In our trial, the incidence of total children movements of 3 groups was 46.81% 22/47 versus 34.88% 15/43 versus 17.78% 8/45, respectively, of DR1, DR2, DR3, which is higher than previous studies reported.[9] However, only a small number of children required to convert to propofol (25.53% 12/47 vs 13.95% 6/43 vs 4.65% 2/45, respectively, of DR1, DR2, DR3). The reason may be mainly due to the different combinations of drugs among these studies.

Comparing the 3 groups, we found that anesthesia onset time was significantly shorter in DR3 group. At the same time, few children in DR3 group needed rescue drugs to complete the flexible bronchoscopy as a result of better hemodynamic stability and synergy sedative mechanism of DEX and RF in high dosage. Though bradycardia and hypotension are the most common adverse reactions during bolus of DEX and RF, unlike previous studies reported, we did not observe the differences among the 3 groups partly because of these being counteracted by premedication in our study.[11,16,17] There were significant differences among the 3 groups in terms of the overall incidence of hypertension, tachycardia, hypoxemia, and cough. As a result, more children in DR1 and DR2 groups need urapidil (36.17% 17/47 vs 20.93% 9/43 vs 11.11% 5/45, respectively, of DR1, DR2, DR3, $P = 0.016$) and esmolol (38.30% 18/47 vs 23.26% 10/43 vs 13.33% 6/45, respectively, of DR1, DR2, DR3, $P = 0.024$) to maintain the hemodynamic stability. The reasons may be mainly due to the different dosages of DEX and RF used in the 3 groups.

The time to recovery for discharge from the PACU was significantly shorter than previous studies reported.[35,36] However, compared with DR1 group, children in DR2 and DR3 groups still stayed longer (10.27 ± 5.21 vs 13.64 ± 5.59 vs 17.23 ± 7.66 min, respectively, of DR1, DR2, DR3, $P = 0.000$). Results from bronchoscopist satisfaction score showed significantly higher in DR2 and DR3 groups than that of DR1 group, which may be due to fewer intraoperative patient movements in DR2 and DR3 groups.

There are several limitations in this study. First, this study is a retrospective trial, multicenter prospective controlled trial is necessary to verify the feasibility of high dosage of DEX-RF used in this children undergoing flexible bronchoscopy. Second, we did not measure the serum concentration of both DEX and RF in this study as a result of short operation time and technical limitation. Third, we did not collect blood gas measurement or transcutaneous capnography in this trial, which may be more accurate to assess respiratory state of children undergoing flexible bronchoscopy.[37,38] Finally, we only discussed 3 different combinations of DEX-RF, studies should be carried out to verify the feasibility of more different doses of DEX-RF used in children undergoing flexible bronchoscopy in the future.

In summary, we first reported that high dose of DEX-RF (DEX infusion at 1.5 μg kg^{-1} for 10 minutes, then adjusted to 0.5–0.7 μg kg^{-1} h^{-1}; RF infusion at 1 μg kg^{-1} for 2 minutes, then adjusted to 0.05–0.2 μg kg^{-1} min^{-1}), which provided better stable hemodynamic profiles and bronchoscopist satisfaction score, less amount of rescue scheme and children movements, could be safely and efficacy used in children undergoing flexible bronchoscopy, though the recovery time was longer.

References

[1] Nicolai T. The role of rigid and flexible bronchoscopy in children. Paediatr Respir Rev 2011;12:190–5.

[2] Goudra BG, Singh PM, Borle A, et al. Anesthesia for advanced bronchoscopic procedures: state-of-the-art review. Lung 2015;193: 453–65.

[3] José RJ, Shaefi S, Navani N. Anesthesia for bronchoscopy. Curr Opin Anaesthesiol 2014;27:453–7.

[4] José RJ, Shaefi S, Navani N. Sedation for flexible bronchoscopy: current and emerging evidence. Eur Respir Rev 2013;22:106–16.

[5] Wahidi MM, Jain P, Jantz M, et al. American College of Chest Physicians consensus statement on the use of topical anesthesia, analgesia, and sedation during flexible bronchoscopy in adult patients. Chest 2011;140:1342–50.

[6] Garnock-Jones KP, Scott LJ. Fospropofol. Drugs 2010;70:469–77.

[7] Dhooria S, Sehgal IS, Aggarwal AN, et al. Diagnostic yield and safety of cryoprobe transbronchial lung biopsy in diffuse parenchymal lung diseases: systematic review and meta-analysis. Respir Care 2016; 61:700–12.

[8] Cutrone C, Pedruzzi B, Tava G, et al. The complimentary role of diagnostic and therapeutic endoscopy in foreign body aspiration in children. Int J Pediatr Otorhinolaryngol 2011;75:1481–5.

[9] Goneppanavar U, Magazine R, Periyadka Janardhana B, et al. Intravenous dexmedetomidine provides superior patient comfort and tolerance compared to intravenousmidazolam in patients undergoing flexible bronchoscopy. Pulm Med 2015;2015:727530.

[10] Fruchter O, Tirosh M, Carmi U, et al. Prospective randomized trial of bispectral index monitoring of sedation depth during flexible bronchoscopy. Respiration 2014;87:388–93.

[11] Chen L, Yu L, Fan Y, et al. A comparison between total intravenous anaesthesia using propofol plus remifentanil and volatile induction/ maintenance of anaesthesia using sevoflurane in children undergoing flexible fibreoptic bronchoscopy. Anaesth Intensive Care 2013;41: 742–9.

[12] Yazbeck-Karam VG, Aouad MT, Baraka AS. Laryngeal mask airway for ventilation during diagnostic and interventional fibreoptic bronchoscopy in children. Paediatr Anaesth 2003;13:691–4.

[13] Simon M, Braune S, Frings D, et al. High-flow nasal cannula oxygen versus non-invasive ventilation in patients with acute hypoxaemic respiratory failure undergoing flexible bronchoscopy-a prospective randomised trial. Crit Care 2014;18:712.

[14] Hong KS, Choi EY, Park DA, et al. Safety and efficacy of the moderate sedation during flexible bronchoscopic procedure: a systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2015;94:e1459.

[15] Pan W, Wang Y, Lin L, et al. Outcomes of dexmedetomidine treatment in pediatric patients undergoing congenital heart disease surgery: a meta-analysis. Paediatr Anaesth 2016;26:239–48.
[16] Liao W, Ma G, Su QG, et al. Dexmedetomidine versus midazolam for conscious sedation in postoperative patients undergoing flexible bronchoscopy: a randomized study. J Int Med Res 2012;40:1371–80.
[17] Ryu JH, Lee SW, Lee JH, et al. Randomized double-blind study of remifentanil and dexmedetomidine for flexible bronchoscopy. Br J Anaesth 2012;108:503–11.
[18] Cook-Sather SD, Harris KA, Chiavacci R, et al. A liberalized fasting guideline for formula-fed infants does not increase average gastric fluid volume before elective surgery. Anesth Analg 2003;96:965–9.
[19] Chadha M, Kulshrestha M, Biyani A. Anaesthesia for bronchoscopy. Indian J Anaesth 2015;59:565–73.
[20] Mason KP, Robinson F, Fontaine P, et al. Dexmedetomidine offers an option for safe and effective sedation for nuclear medicine imaging in children. Radiology 2013;267:911–7.
[21] Malik JA, Gupta D, Agarwal AN, et al. Anticholinergic premedication for flexible bronchoscopy: a randomized, double-blind, placebo-controlled study of atropine and glycopyrrolate. Chest 2009;136: 347–54.
[22] Walters DM, Wood DE. Operative endoscopy of the airway. J Thorac Dis 2016;8(suppl 2):S130–9.
[23] Kaur H, Dhooria S, Aggarwal AN, et al. A randomized trial of 1% vs 2% lignocaine by the spray-as-you-go technique for topical anesthesia during flexible bronchoscopy. Chest 2015;148:739–45.
[24] Antoniades N, Worsnop C. Topical lidocaine through the bronchoscope reduces cough rate during bronchoscopy. Respirology 2009;14:873–6.
[25] Contoli M, Gnesini G, Artioli D, et al. Midazolam in flexible bronchoscopy premedication: effects on patient-related and procedure-related outcomes. J Bronchology Interv Pulmonol 2013;20:232–40.
[26] Rolo R, Mota PC, Coelho F, et al. Sedation with midazolam in flexible bronchoscopy: a prospective study. Rev Port Pneumol 2012;18:226–32.
[27] Wang H, Yang C, Zhang B, et al. Efficacy of target-controlled infusion of propofol and remifentanil with high frequency jet ventilation in fibre-optic bronchoscopy. Singapore Med J 2013;54:689–94.
[28] Grendelmeier P, Tamm M, Pflimlin E, et al. Propofol sedation for flexible bronchoscopy: a randomised, noninferiority trial. Eur Respir J 2014; 43:591–601.
[29] Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. Am J Emerg Med 2008;26:985–1028.
[30] Purugganan RV. Intravenous anesthesia for thoracic procedures. Curr Opin Anaesthesiol 2008;21:1–7.
[31] Song IA, Seo KS, Oh AY, et al. Dexmedetomidine injection during strabismus surgery reduces emergence agitation without increasing the oculocardiac reflex in children: a randomized controlled trial. PLoS One 2016;11:e0162785.
[32] Zamani MM, Keshavarz-Fathi M, Fakhri-Bafghi MS, et al. Survival benefits of dexmedetomidine used for sedating septic patients in intensive care setting: a systematic review. J Crit Care 2016;32:93–100.
[33] Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. Br J Anaesth 2015;115:171–82.
[34] Irwin MG, Wong GT. Remifentanil and opioid-induced cardioprotection. J Cardiothorac Vasc Anesth 2015;29(suppl 1):S23–6.
[35] Ge DJ, Qi B, Tang G, et al. Intraoperative dexmedetomidine promotes postoperative analgesia and recovery in patients after abdominal colectomy: a CONSORT-prospective, randomized, controlled clinical trial. Medicine (Baltimore) 2015;94:e1727.
[36] Lo YL, Lin TY, Fang YF, et al. Feasibility of bispectral index-guided propofol infusion for flexible bronchoscopy sedation: a randomized controlled trial. PLoS One 2011;6:e27769.
[37] Conway A, Douglas C, Sutherland JR. A systematic review of capnography for sedation. Anaesthesia 2016;71:450–4.
[38] Nassar BS, Schmidt GA. Capnography during critical illness. Chest 2016;149:576–85.