The clinical safety and efficacy of flexible bronchoscopy in a neonatal intensive care unit

CHONGBING YAN, YONG HU, GANG QIU, XIAOHUI GONG and DERMYSHI ELDA

Department of Neonatology, Shanghai Children's Hospital, Shanghai 200062, P.R. China

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Abstract. Flexible bronchoscopy (FB), developed in the 1960s, is widely used in the clinical practice of pediatrics and has demonstrated fundamental value in clinical diagnoses and treatment. However, as an invasive procedure, the use of FB is limited due to concerns regarding the tolerance of the procedure and the possible complications in neonatal units. Thus, the present study aimed to investigate the clinical safety and efficacy of flexible bronchoscopy (FB) in a neonatal intensive care unit (NICU). Neonates (n=54) who received FB in the NICU of Shanghai Children's Hospital between January 2012 and December 2016 were enrolled as the experimental group and another 54 neonates who required nebulization and tracheal secretion suction treatments were the control group. Indicators including blood gas, complete blood count, C-reactive protein (CRP), X-ray, patient breathing rate, temperature and blood pressure were monitored prior to and following the procedure. No significant differences in sex, gestational age, birth weight or postnatal age were observed between the experimental group and the control group (P>0.05). Among the 54 FB patients, several cases with side effect were identified, including 18 (33.3%) with respiratory tract stenosis, nine (16.7%) with malacia and stenosis and six (11.1%) with esophagotracheal fistula. Among the 54 members of the control group, 44 neonates (81.4%) were discharged with improved condition, five (9.3%) succumbed and five patients (9.3%) abandoned the treatment and left the hospital. Bronchoalveolar lavage demonstrated consistent results with respiratory secretion culture or tracheal tube culture. In comparison between the experimental and the control groups, no significant difference in pH, partial pressure of carbon dioxide (PCO_2), partial pressure of oxygen (PO_2) and HCO_3^- was observed, while there were no statistical differences in the values of pH, PCO_2 and HCO_3^- (P>0.05). However, PO_2 was significantly increased, and CRP was significantly reduced, following FB procedure compared with prior to FB (P<0.05). No pneumothorax, shock, other severe complications, fever or diffused pneumonia were observed during or after FB. The data from the present study demonstrated that FB is a safe and effective strategy for the diagnosis and differentiation of neonatal respiratory diseases in NICU.

Correspondence to: Dr Yong Hu, Department of Neonatology, Shanghai Children's Hospital, 355 Luding Road, Shanghai 200062, P.R. China
E-mail: yonghu33x@163.com

Key words: flexible bronchoscopy, neonatal intensive care unit, tracheomalacia, bronchoalveolar lavage, esophagotracheal fistula

Introduction

Flexible bronchoscopy (FB) was developed in the 1960s. The principle mechanism is that light, originating from an external source, is transmitted into the airway by optical waveguide fiber (1,2). The endoscopic field can be observed by eye, or in the case of modern bronchoscopic devices, on a monitor. The condition of trachea and bronchia can be clearly observed and determined by observation. FB functions as an important diagnostic tool to identify the etiology of respiratory diseases (3). Some abnormalities, such as tracheal-malacia or stenosis, which cannot be diagnosed by radiological images, can be confirmed by FB (4). It can also be used to move foreign bodies in the respiratory tract. Currently, FB is widely used in the clinical practice of pediatrics (Table I). It has demonstrated fundamental value in clinical diagnoses and treatment (5,6). However, as an invasive procedure, the use of FB is limited due to concerns regarding the tolerance of the procedure and the possible complications in neonatal units. The purpose of the present study was to evaluate the safety and efficacy of FB in the neonatal intensive care unit (NICU).

Subjects and methods

Neonates and criteria. A total of 54 FB neonates admitted to the NICU of Shanghai Children's Hospital (Shanghai, China) between January 2012 and December 2016 were enrolled in the present study according to the Pediatric Bronchoscopy Guidelines (6). Among the 54 FB neonates in experimental group, 37 (68.5%) were male and 17 (31.5%) were female. Gestational age ranged from 207 to 290 days (261.87±19.72 days). The birth weight ranged from 1,300 to 4,400 g (2,889.63±675.55 g). The postnatal age ranged from 2 to 290 days (29.2±27.79 days). Inclusion criteria were neonates with recurrent dyspnea or suspicious

respiratory tract anomaly; with recurrent pulmonary infection or atelectasis in the same lung lobe; with suspicious tracheal stenosis in radiological image [X-ray or computed tomography (CT) scan]; inability to be extubated without clear reason; or confirmed congenital esophageal atresia to clarify the presence and position of esophagobronchial fistula before surgery (Fig. 1). Exclusion criteria were multiple organ dysfunction; severe respiratory diseases with high values of ventilation; severe congenital heart disease or cardiac function failure; coagulopathy; present hyperthermia; or preterm weight <1,500 g. Data were recorded in detail, including gestational age, postnatal age, birth weight, corrected gestational age while receiving FB, hospital stays, ventilation status and outcomes. Vital signs reflecting FB procedure, such as breathing rate, heart rate and oxygen saturation (SaO_2), were monitored. Bronchoalveolar lavage (BAL) was performed when signs of endobronchitis were identified, and BAL fluid was sampled for laboratory tests including cell count, biochemistry and culture. Indicators including blood gas, CBC, CRP and X-ray at 1 h before and 1 h after FB were ascertained. Patient breathing rate, temperature and blood pressure following FB were recorded. Another 54 neonates who required nebulization treatment and tracheal secretion suction were set as the control group. The neonates were also admitted to the NICU of Shanghai Children's Hospital (Shanghai, China) between January 2012 and December 2016. Among the 54 FB neonates, 36 (66.7%) were male and 18 (33.3%) were female. The birth weight ranged from 1,250 to 4,500 g (2,921.26±743.96 g). The postnatal age ranged from 4 to 282 days (31.45±25.67 days). The present study was reviewed and approved by the Ethics Committee of Shanghai Children's Hospital, China (approval no. 2011-231). All families who participated in the present study voluntarily signed informed consent. The primary diseases diagnosed in the control group were pneumonia, neonatal respiratory distress syndrome and wet lung.

The Olympus BFXP40 bronchoscope (Olympus Corp.) was used for FB. The outer diameter of the probe was 2.8 mm, with a 1.2 mm operation tunnel. In addition to using the probe to observe the trachea and bronchia, the operation tunnel, through which oxygen suction can be conducted, was employed for BAL. Patients did not eat from 4 h before FB to prevent vomiting and aspiration during the procedure. In case of complications, such as laryngeal edema, laryngospasm, or pneumothorax, the FB procedure was performed in the resuscitation unit of the NICU. In addition to a bedside oxygen inhalation tube, a tracheal tube, a resuscitation mask and a suction machine were made ready. Midazolam was used as sedation, with 0.1-0.3 mg/kg intravenous injection adopted prior to the FB procedure. During the FB, midazolam 0.1 mg/kg/h intravenous infusion was administered, and lidocaine hydrochloride mucilage was administered as local anesthesia. The patients received oxygen by nasal tube during the procedure.

Statistical analysis. All the statistical analyses were performed using SPSS 17.0 software (SPSS, Inc.). Unpaired Student's t-test was used for the comparison between twogroups and χ^2 test was used for enumeration data. P<0.05 was considered to indicate a statistically significant difference.

Table I. Applications of flexible bronchoscopy.

1	Tracheal, bronchial, pulmonary dysplasia or abnormity. Primary alterations include laryngomalacia, tracheobronchomalacia, laryngeal stenosis, tracheobronchial stenosis and esophagotracheal fistula. Secondary alterations include tracheobronchial compression caused by subglottic hemangioma, pulmonary artery sling, vascular ring, cardiac dilatation, and stenosis caused by intubation.
2	Atelectasis; using bronchoscopy to check and/or offer bronchoalveolar lavage
3	Hemoptysis or blood-stained sputum, using bronchoscopy to investigate the pathogen and perform pathological examination
4	Chronic cough and recurrent respiratory infection
5	Recurrent or persistent stridor or wheezing
6	Diffused or focal lesions in the lungs
7	Pulmonary tuberculosis
8	Removal of foreign bodies
9	Assistance in diagnosis in some thoracic surgery
10	Assistance in difficult intubations
11	Other treatments including cryotherapy, interventional therapy and balloon dilatation therapy

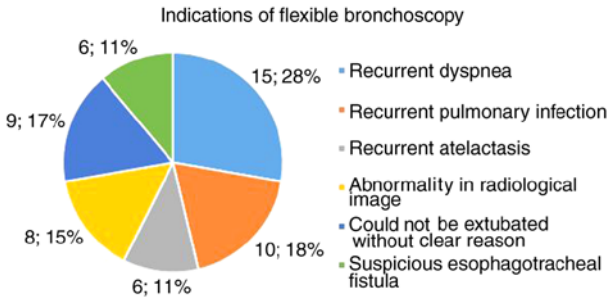

Figure 1. Indications for bronchoscopy. Recurrent dyspnea, 15 cases; Recurrent pulmonary infection, 10 cases; Recurrent atelectasis, 6 cases; Abnormality in radiological image, 8 cases; Could not be extubated without clear reason, 9 cases; Suspicious esophagotracheal fistula, 6 cases.

Results

General data. A total of 56 FB procedures were conducted with 54 neonates, among whom two received FB twice. Among the 54 neonates, 33 (61.1%) used ventilation and 12 (22.2%) used nasal continuous positive airway pressure; 8 cases received the FB procedure with intubation. No significant differences in sex, gestational age, birth weight or postnatal age were observed between the experimental and the control groups (P>0.05; Table II).

Results of FB. Among the 54 FB patients, 44 (81.5%) were identified with varying degrees of airway abnormality. Endobronchitis was observed in 9 cases (16.7%), while there was only 1 case (1.8%) without any abnormalities. During the

Table II. General data.

Characteristics	Experimental group (n=54)	Control group (n=54)	χ^2 or t-test	P-value
Sex (male/female)	37/17	34/20	0.37	0.54
Gestational age (days)	261.87±19.72	263.56±18.31	0.46	0.65
Birth weight (g)	2889.63±675.55	2915.72±688.31	0.2	0.84
Postnatal age (days)	29.2±27.79	28.36±27.45	0.16	0.87

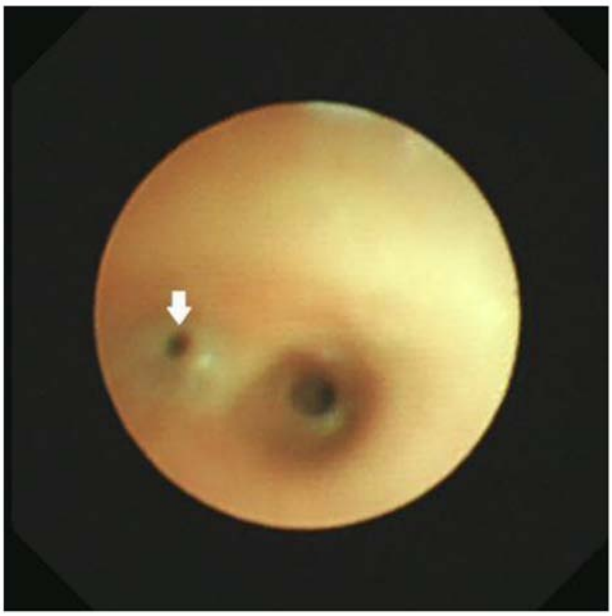

Figure 2. Esophagotracheal fistula. Arrow indicates the fistula.

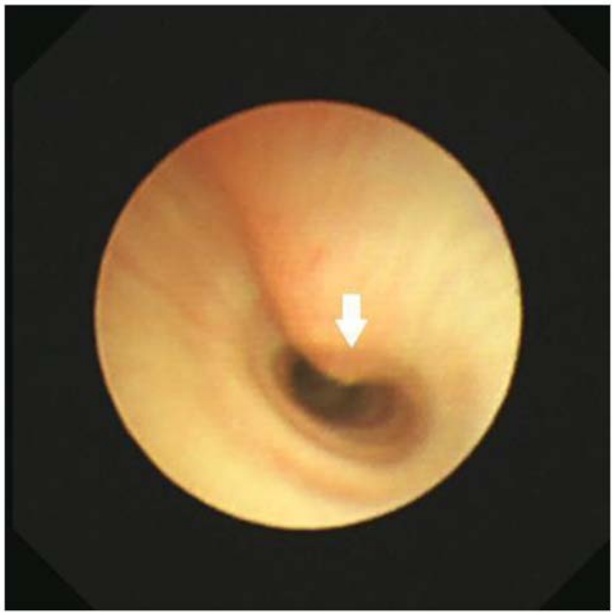

Figure 3. Tracheal stenosis by external pressure. Arrow indicates the respiratory tract stenosis.

procedure, it was noticed that in 3 patients the probe of FB could not pass through the glottis; one case presented severe epiglottis malacia and severe glottic stenosis was detected in 2 cases. There were 27 patients (50%) with different degrees of respiratory tract malacia and 18 (33.3%) exhibited different degrees of respiratory tract stenosis. In addition, 9 cases (16.7%) were diagnosed with both malacia and stenosis while 6 cases (11.1%) had esophagotracheal fistula (Figs. 2-7).

Outcomes. In the experiment group, 44 neonates (81.4%) were discharged with improved condition, 5 (9.3%) succumbed and 5 (9.3%) abandoned the treatment and left the hospital. Among the patients who were discharged, 3 were treated with a tracheostomy and went home with trachea cannula and 1 presented with epiglottic anomaly and the FB could not pass the vocal cord. The other 2 cases presented laryngomalacia combined with trachobronchomalacia. Among the 5 mortalities, 1 was identified with severe glottic stenosis and the FB could not pass, 1 was observed with multiple-malformations of bones, annular stenosis at the middle of trachea, stenosis at the opening of bilateral main bronchi and severe stenosis at left lower bronchus. Severe endobronchitis with tracheal stenosis, mild bronchomalacia with endobronchitis, bronchomalacia combined with stenosis at the left main bronchus were observed in the other 3 cases, respectively. These last 3 cases were all intubated, but succumbed as parents decided to relinquish all medical treatments. In all, 34 cases were examined by X-ray or CT scan prior to and following FB and improvement on the radiological images was observed in 21 cases (61.8%).

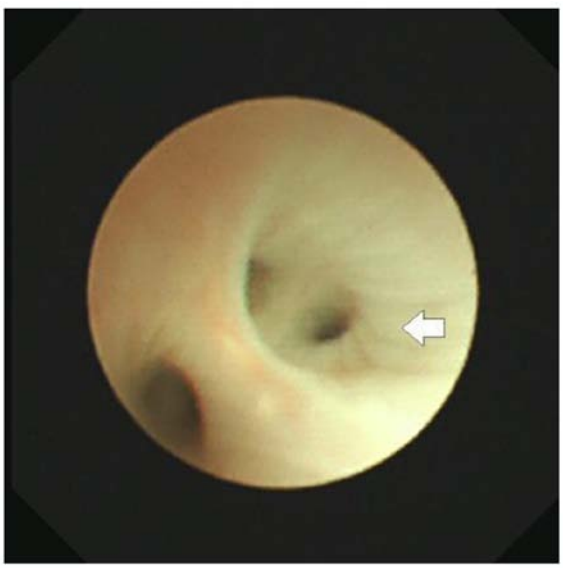

Figure 4. Endobronchitis (pale mucosa with floc). Arrow indicates the manifestation of endobronchitis.

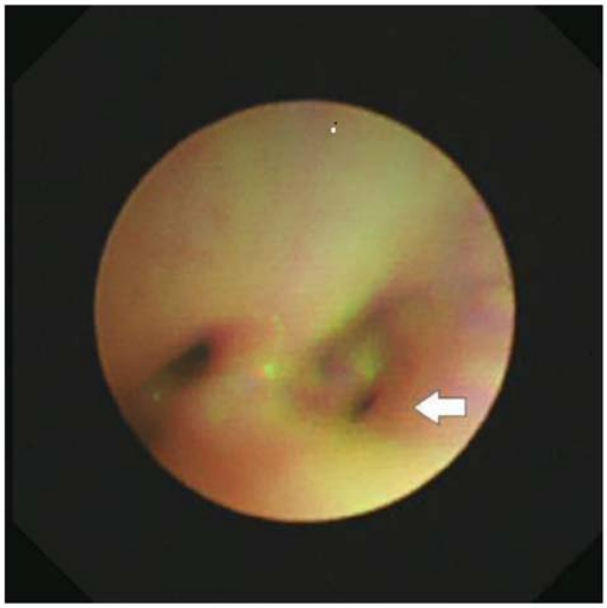

Figure 5. Bronchial stenosis. Arrow indicates the respiratory tract stenosis.

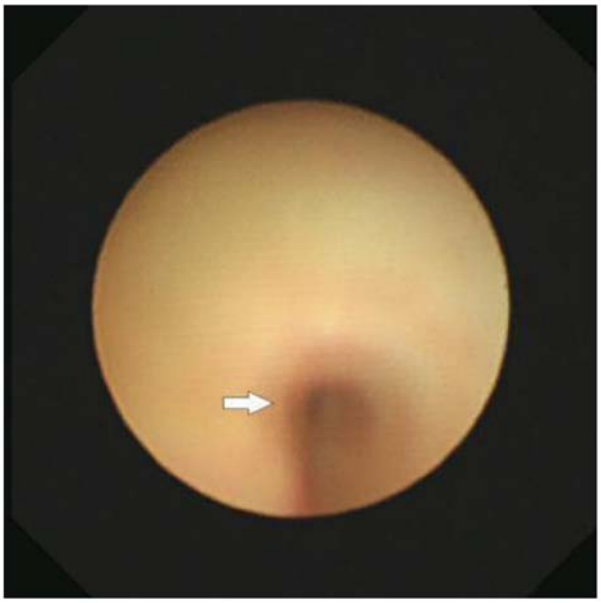

Figure 7. Bronchomalacia. Arrow indicates the severe epiglottis malacia.

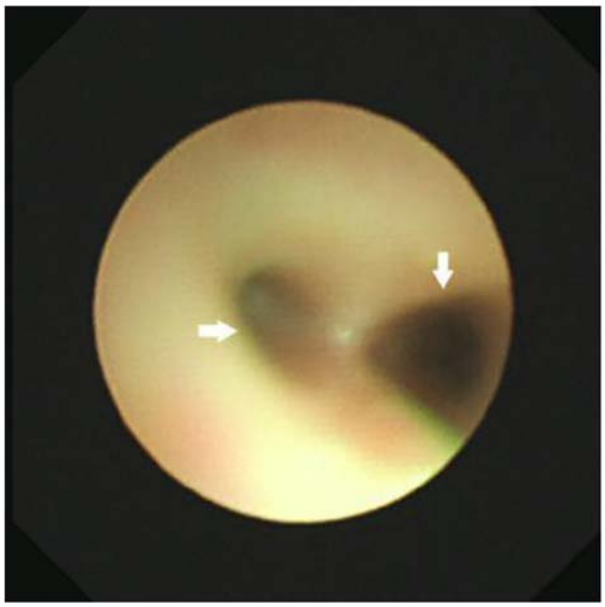

Figure 6. Stenosis at the opening of left main bronchus. Both arrows indicate the respiratory tract stenosis.

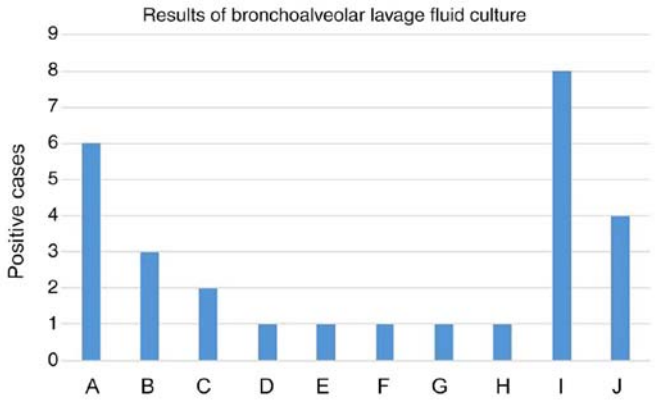

Figure 8. Results of bronchoalveolar lavage fluid culture. A, *Acinetobactor baumanii*; B, *Klebsiella pneumoniae*; C, *Pseudomonas aeruginosa*; D, *Klebsiella oxytoca*; E, *Escherichia coli*; F, *Staphylococcus haemolyticus*; G, *Stenotrophomonas maltophilia*; H, *Enterobacter cloacae*; I, *Streptococcus viridans* and/or *Neisseria*; J, Negative.

BAL. Among the 54 patients, 28 received BAL. BAL fluid samples were collected for cell counts, biochemistry and culture test. For the BAL fluid culture, 24 cases tested as positive (85.7%) while 4 were negative (14.3%). Consistent results between the BAL fluid culture and respiratory secretion culture or tracheal tube culture were identified in 21 cases (75%; Fig. 8).

Safety of FB. Blood gases were detected at 1 h before and 1 h after FB for the patients in the experimental group. The results demonstrated that there were no statistical differences in the values of pH, partial pressure of carbon dioxide (PCO_2) and HCO_3^-. However, partial pressure of oxygen (PO_2) was significantly higher following FB procedure compared with that prior to FB ($P<0.05$; Table III). Blood gases were also tested at 1 h before and 1 h after atomization and secretion suction in the patients of the control group. The results demonstrated that there were no significant differences in pH, PCO_2, PO_2 and HCO_3^- (Table IV). In comparison between the experimental group and control group, no significant difference in pH, PCO_2, PO_2 and HCO_3^- was observed (Table V). No statistical differences were observed in white blood cell count, hemoglobin, platelet count and neutrophil ratio prior to and following FB. Notably, CRP was significantly decreased following FB ($P<0.05$; Table VI).

Complications. During the 56 FB procedures performed on 54 patients, SaO_2 decreased to ~80% in 13 cases (23.3%). After a transient pause, oxygen suction was provided through the

Table III. Blood gas analysis before and after flexible bronchoscopy.

Blood gas	Before	After	t-test	P-value
pH	7.39±0.08	7.40±0.07	-0.627	0.535
PCO_2 (mmHg)	49.03±9.95	47.78±11.39	0.791	0.434
PO_2 (mmHg)	46.83±13.36	58.32±24.10	-2.688	0.011
HCO_3^- (mmol/l)	28.77±5.07	29.19±5.00	-0.787	0.436

n=38, P<0.05 was considered to indicate a statistically significant difference. PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen.

Table IV. Blood gas analysis before and after atomization and secretion suction.

Blood gas	Before	After	t-test	P-value
pH	7.35±0.10	7.36±0.09	-1.477	0.148
PCO_2 (mmHg)	47.93±12.47	45.65±10.66	1.253	0.218
PO_2 (mmHg)	44.95±19.88	48.3±17.22	-1.556	0.128
HCO_3^- (mmol/l)	25.70±3.29	25.63±3.40	0.175	0.862

n=38, P<0.05 was considered to indicate a statistically significant difference. PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen.

Table V. Blood gas analysis comparison between experimental and control groups.

Blood gas	Experimental group	Control group	t-test	P-value
pH	-0.01±0.09	-0.02±0.07	0.426	0.672
PCO_2 (mmHg)	1.25±9.74	2.28±11.22	-0.380	0.706
PO_2 (mmHg)	-11.5±26.37	-3.35±13.28	-1.707	0.096
HCO_3^- (mmol/l)	-0.43±3.33	0.07±2.41	-0.756	0.455

n=38, P<0.05 was considered to indicate a statistically significant difference. PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen.

Table VI. Complete blood count and CRP before and after flexible bronchoscopy.

Complete blood count	Before	After	t-test	P-value
White blood cells (10^9/l)	14.31±5.62	13.42±5.84	1.363	0.179
Hemoglobin (g/l)	135.28±29.36	131.44±32.28	1.397	0.169
Platelets (10^9/l)	382.94±170.24	385.42±158.37	-0.187	0.852
Neutrophils (%)	54.62±14.15	50.86±16.57	1.987	0.053
CRP (mg/l)	6.06±10.90	4.04±6.29	2.335	0.024

n=50, P<0.05 was considered to indicate a statistically significant difference. CRP, C-reactive protein.

operation tunnel and SaO_2 increased quickly in all 13 cases. The patients in all 13 cases could tolerate the intervention until FB was completed. Mild tracheal or bronchial mucosa hemorrhage occurred in 13 cases (23.3%), but no case presented severe bleeding. No pneumothorax, shock or other severe complications, which might impede the procedure were identified. No fever or diffused pneumonia was observed following FB.

Discussion

Flexible bronchoscopy (FB) has developed rapidly in pediatrics in recent years (7). In addition to the value of observation and diagnosis as endoscopy, FB can be used to remove foreign bodies, provide guidance for bronchoalveolar lavage (BAL), intubation and balloon dilatation surgery and as a tool for treatments (5,6). At present, there are four different models of bronchoscope in pediatrics. The inner diameters are 4.9, 3.5, 2.8 and 2.2 mm, respectively, with optional operation tunnels. The smallest one is the 2.2-mm diameter probe with no operation tunnel, which can only be used to observe and diagnose. The 2.8-mm diameter probe is widely used in neonatal wards, because it can be operated through a 3.5 or 4 mm tracheal tube and can be accompanied with an operation tunnel for oxygen supply. Continuous or recurrent dyspnea and stridor frequently occur in some patients in NICU. Occasionally the confirmatory diagnosis cannot be made by regular radiological examination. For these patients, FB presents an alternative to detect anomalies of the respiratory tract. He *et al* (8) reported that pathological changes were identified in 73 cases out of 82 patients (89.0%), in which 24 cases were diagnosed with congenital respiratory tract malformations (39.3%). In the present study, respiratory construction problems were identified in 44 cases out of 54 patients (81.5%). In NICU, due to different reasons, many clinically indicated neonates cannot receive FB examination: It may lead to misdiagnosis and affect the treatment outcomes, resulting in a high positive rate of anomalies.

Respiratory tract malacia, including laryngomalacia, tracheomalacia and bronchomalacia, represents the most common respiratory malformation (9). In neonates and children with stridor, the morbidity of laryngonalacia is 60-70% (10). The majority of patients with laryngomalacia do not require intervention. However, some severe cases can progress to pulmonary hypertension and pulmonary heart disease due to a lack of appropriate treatments. As laryngonalacia is poorly tolerated in 10% of cases, assessment and surgical management as well as management of any associated gastro-esophageal reflux are often required to effectively control symptoms (11). For instance, 5-20% of children with severe or refractory disease may require a more aggressive intervention, most commonly in the form of transoral supraglottoplasty (12). Erdem *et al* (13) reported that in 109 infants with stridor, 37 cases were identified with isolated laryngomalacia, 54 cases with laryngomalacia with secondary airway lesions, including tracheomalacia, bronchomalacia and tracheobronchomalacia. Only 19 patients received surgery, of which 12 had a tracheostomy. The present study identified 14 patients with laryngomalacia, of which three received tracheostomy. However, Olney *et al* (14) recommended that FB should not be routinely performed in laryngomalacia; only if there is evidence of concomitant airway lesion. The symptoms of tracheobronchomalacia are not distinctive, but it is the most common cause of recurrent stridor and cough in infants. According to its etiology, tracheomalacia can be divided into two types: Primary tracheomalacia and secondary tracheomalacia. Primary tracheomalacia is a congenital condition. It may represent an isolated finding or be associated with other congenital anomalies, such as cleft palate, choanal atresia and esophageal atresia. Secondary tracheomalacia is always caused by trauma, extratracheal compression, positive pressure ventilation, respiratory tract infection or inflammation (15). In preterms with bronchopulmonary dysplasia, secondary tracheomalacia is very common (16). The present study identified 19 cases of tracheomalacia, bronchomalacia or tracheobronchomalacia out of 54 patients (35.2%). Neonates with respiratory tract malacia will progress to obstruction with secretion following airway infection. Malacia can lead to dyspnea, atelectasis, recurrent respiratory infection and difficulty in extubation. Therefore, the positive rate of respiratory tract malacia is high in the indicated neonates of FB. The majority of these patients require only supportive treatments, but some, who have severe symptoms of obstruction, may require surgery (17-19). Congenital heart disease is the main reason for secondary tracheomalacia and tracheal stenosis. Lee *et al* (20) reported that in the children with congenital heart disease and respiratory obstructive problems, 67% of them were diagnosed by FB with tracheal stenosis due to extratracheal compression. The present study identified two cases with tracheal stenosis caused by extratracheal compression associated with a large ventricular septal defect. FB is also important to surgical departments. It offers useful assistance for thoracic, otolarynological and some general surgeries (21-24).

BAL can remove the secretion in the respiratory tract to remove obstructions. BAL fluid culture provides confirmatory identification of the specific pathogen and guides the anti-infection treatment. The testing of BAL fluid is an important method to assist clinic diagnosis and predict outcomes (25-27). Currently the research on BAL has moved from the cellular to the molecular level (28-30).

There remains a safety concern about FB in neonatal units and complications of FB are frequently identified, including laryngeal edema, laryngeal spasm, hemorrhage, pneumothorax or mediastinal emphysema, hypoxia and fever (31). However, in pediatric clinical practice, severe complications rarely happen (32). It is even safe for patients who receive extracorporeal membrane oxygenation treatment (33). Soong *et al* (34) reported that the oxygen supplied by using nasopharyngeal catheter during FB is a simple and cost-effective method to maintain appropriate SaO_2. In line with the previous findings, the present study illustrated the favorable improvements due to FB in neonates, although there were a number of side effects during the procedure. Overall, 44 neonates (81.4%) were discharged with an improved condition, 5 cases (9.3%) succumbed and 5 patients (9.3%) abandoned the treatment and left the hospital. Overall, no significant difference in terms of pH, PCO_2, PO_2 and HCO_3^- was identified between the experimental and control groups. However, PO_2 was significantly increased, whereas CRP was significantly reduced following FB procedure compared with prior to FB ($P<0.05$). No fever or diffused pneumonia was observed following FB. A limitation in the present study was that the clinical safety requires further validation with a larger number of patients in NICU. As for the sedation during the FB procedure, midazolam in combination with

fentanyl or alfentanil is the first choice (28). More studies are required to examine the best way to decrease damage caused by FB in neonates.

In conclusion, FB possesses important value in diagnosis and differentiation in neonatal respiratory diseases. BAL can be a useful treatment in atelectasis. FB is relatively safe in clinical practice in NICU and severe complications rarely occur.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CY and YH contributed to the conception and design of the study and performed the experiments. GQ, XG and DE contributed to acquisition, analysis and interpretation of data. CY drafted the manuscript and revised it critically for important intellectual content and gave final approval of the version to be published. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was reviewed and approved by the Ethics Committee of Shanghai Children's Hospital, Shanghai, China (approval no. 2011-231). All families participated in the present study voluntarily and signed informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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