Bronchoalveolar lavage under ultrasound monitoring of lungs for the treatment of neonatal atelectasis and lung consolidation

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Abstract. Neonatal atelectasis and pulmonary consolidation diseases are common and difficult to treat. Thus, novel treatment methods need to be explored. Although an X-ray chest radiography is feasible for the detection of neonatal atelectasis and pulmonary consolidation diseases, there is a risk of radiation damage and lung ultrasound may be used instead. The aim of the present study was to investigate the bronchoalveolar lavage (BAL) under ultrasound monitoring of lungs for the treatment of neonatal atelectasis and lung consolidation disease. For this purpose, the present study prospectively selected 73 children with severe newborn respiratory distress syndrome (NRDS), 60 children with severe neonatal pneumonia (NP), and 65 children with meconium aspiration syndrome (MAS) as the research subjects. Each disease was divided into three groups as follows: The exogenous pulmonary surfactant (PS) lavage group, the normal saline (NS) lavage group and the non-lavage group, using lung ultrasound as the imaging method for lung disease. The treatment effect, complications and differences in the oxygenation index (OI) among the three groups of each disease were compared. The results revealed that the time of lung recruitment and invasive ventilator treatment among the three groups of each disease was shorter in the PS lavage group than in the NS lavage group, and also between the PS lavage and NS lavage group compared with the non-lavage group (P<0.05). Following treatment for each disease, the PS lavage group exhibited a more rapid decline in OI than the NS lavage group, and the PS lavage group and NS lavage group exhibited a more rapid decline in OI than the non-lavage group (P<0.05). No significant differences in treatment complications were observed among the three groups of each disease (P>0.05). On the whole, the present study demonstrates that BAL under lung ultrasound monitoring is effective in the treatment of neonatal atelectasis and pulmonary consolidation diseases caused by severe NRDS, severe NP or MAS. It can decrease the invasive ventilator treatment time of neonatal atelectasis and lung consolidation more rapidly, and can rapidly decrease the OI, without increasing complications. Thus, exogenous PS lavage is more effective than NS lavage.

Introduction

Neonatal lung ultrasound images of severe newborn respiratory distress syndrome (NRDS), severe neonatal pneumonia (NP) and meconium aspiration syndrome (MAS) mainly reveal atelectasis and lung consolidation, and it is difficult to distinguish these diseases based on the performance of lung ultrasound alone (1,2). Neonatal atelectasis and lung consolidation are common complications of severe NRDS, severe NP and MAS. The purpose of treatment is lung recruitment. An X-ray chest radiography is typically conducted to determine whether the lung has been recruited again; however, there is a risk of radiation damage. Therefore, a clinical evaluation technique without the risk of radiation damage is required (1,3-5). In recent years, some scholars have proposed the use of lung ultrasound to examine lung diseases (6-10). The treatment of neonatal atelectasis and lung consolidation diseases is difficult, and novel treatment methods thus need to be explored. Bronchoalveolar lavage (BAL) is known to be effective in the treatment of neonatal atelectasis and lung consolidation diseases; however, available related studies are limited (11,12). To the best of our knowledge, to date there is no comprehensive study of BAL in the treatment of severe NRDS, severe NP and MAS. Therefore, the present prospective study aimed to provide a reference for the clinical application of BAL in the treatment of neonatal atelectasis and lung consolidation diseases under lung ultrasound monitoring.

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Patients and methods

Patients. The present prospective study was conducted at the Level 3 neonatal intensive care unit (NICU) of the Department of Neonatology, Kunming Medical University, Kunming, China. The study was approved by the Medical Ethics Committee of the Dehong People's Hospital Affiliated to Kunming Medical University, and signed informed consent was obtained from the guardians of the children. The research subjects included 73 cases of severe NRDS, 60 cases of severe NP and 65 cases of MAS admitted to the Level 3 NICU of the Department of Neonatology, Kunming Medical University between March, 2018 and December, 2020. Lung ultrasound was used as the imaging method for lung disease (Table I).

Diagnosis and treatment. Disease diagnosis, treatment, initial parameter setting of invasive mechanical ventilation, adjustment during treatment, invasive mechanical ventilation combined with inhaled nitric oxide (INO) treatment, continuous renal replacement therapy (CRRT) and the application of exogenous pulmonary surfactant (PS) (PS for Poractant Alfa Injection, Chiesi Farmaceutici S.p.A.) were all based on the published guidelines and 'Pediatric mechanical ventilation' (1,7,13,14).

Inclusion and exclusion criteria. The inclusion criteria were the following: For severe NRDS: i) An age <12 h; ii) invasive mechanical ventilation-assisted ventilation was required; iii) atelectasis, lung consolidation ≥2 intercostal spaces; iv) diagnosis of severe NRDS. For severe NP: i) An age ≤28 days; ii) invasive mechanical ventilation-assisted ventilation was required; iii) atelectasis, lung consolidation ≥2 intercostal spaces; iv) diagnosis of severe NP. For MAS: i) An age <24 h; ii) invasive mechanical ventilation-assisted ventilation was required; iii) atelectasis, lung consolidation ≥2 intercostal spaces; iv) diagnosis of MAS. The exclusion criteria were as follows: i) Complicated with congenital heart disease; ii) grade III-IV intracranial hemorrhage; iii) diaphragmatic hernia, swollen diaphragm; iv) hemophilia, VitK1 deficiency; v) lung isolation syndrome; vi) pulmonary hemorrhage.

Research methods and observation. An ultrasonic examination of the neonatal lungs was conducted using probes with a frequency of 5-15 MHz, with >9.0 MHz being more commonly used (15,16). Infected patients were treated with sensitive antibiotics, severe renal impairment was treated with CRRT, and those with concomitant persistent pulmonary hypertension of the newborn (PPHN) were treated with a combination of inhaled nitric oxide (INO) (17). The lavage method invovled the following procedures: i) Complete tracheal intubation before lavage, and fully remove meconium before lavage for MAS; ii) the PS lavage group was irrigated twice with normal saline (NS) at 1.5 ml for premature infants, NS at 3 ml for full-term infants, and the third lavage with exogenous PS 50 mg/kg + NS; NS capacity (ml) is the same as PS calculation capacity (ml); the NS lavage group was irrigated three times with NS alone 1.5 ml for premature infants, NS 3 ml for full-term infants; iii) balloon-connected tracheal tube ventilation or mechanical ventilation higher than the normal 2 cmH$_2$O peak inspiratory pressure (PIP) was administered

for 2-5 min following the injection of lavage fluid (18); iv) the vital signs of the child were monitored throughout the lavage; it was ensured that the child exhibited no hypoxia during lavage; v) efforts were made to ensure the quality of the lavage, but also to ensure the operation was performed in a skilled and sensitive manner. For PS treatment after lavage, an intratracheal infusion of 100 mg/kg of exogenous PS was administered within 10 min following alveolar lavage. The non-lavage group was directly administered exogenous PS at 100 mg/kg via intratracheal instillation. Treatment follow-up and PS application involved the following: i) Lung recruitment index: The range and extent of atelectasis and lung consolidation as revealed by the lung ultrasound image were reduced; ii) lung ultrasound was reviewed 2-4 h following lavage to monitor lung recruitment; when there was no obvious lung recruitment in 24 h, a second infusion of exogenous PS at 100 mg/kg was administered via intratracheal instillation. When there was no obvious lung recruitment in 48 h, a third infusion of exogenous PS at 100 mg/kg was administered via intratracheal instillation. The indications for the withdrawal of the invasive ventilator were the following: i) The cause of respiratory failure had been relieved or was being relieved; ii) the airway was unobstructed, the cough reflex was obvious, and the strength of the respiratory muscles was restored; spontaneous breathing was strong (active), with sputum suction tolerance; iii) the ventilator parameters were already low: Fraction of inspired O$_2$ (FiO$_2$) <40%, respiratory rate (RR) <15 beats/min, PIP <15 cmH$_2$O, positive end-expiratory pressure (PEEP) <4 cmH$_2$O and arterial blood gas analysis was normal; iv) under lower ventilator parameters the lung ultrasound examination prompted two consecutive times to indicate that the lung had been recruited, and the interval between the two examinations was ≥4 h; v) the circulatory state was stable and did not rely on circulating drugs; vi) no muscle relaxants were within 12 h. The aforementioned conditions had to be met simultaneously in order invasive ventilator therapy to be withdrawn. For observations and comparisons, the differences in treatment effects, complications and the oxygenation index (OI) among the three groups for each disease.

Statistical analysis. The data were analyzed using SPSS 25.0 software (SPSS, Inc.), and the measurement data that conformed to the normal distribution are expressed as the mean ± standard deviation (mean ± SD). Comparisons among multiple groups were performed using one-way ANOVA., and with the least significant difference (LSD) post hoc test. Count data are expressed as a percentage; significant differences in rates were tested using a Chi-squared test or Fisher's exact probability test. A P-value <0.05 was considered to indicate a statistically significant difference.

Results

No statistically significant differences were found in the general data among the three groups (P>0.05) (Table I), comparable among the three groups. The difference in lung recruitment time and invasive ventilator treatment time among the three groups was statistically significant (P<0.05). The PS lavage group exhibited a shorter time than the NS lavage group, and the PS lavage group and NS lavage group exhibited

Table I. Comparison of general information of the three groups.

Group	PS lavage group	NS lavage group	No lavage group	F/χ^2 value	P-value
Severe NRDS	22	24	27		
Male	12	11	14	0.37	>0.05
Gestational week	30.77±2.47	30.55±2.58	31.29±3.45	0.4391	>0.05
Birth weight (kg)	1.587±0.539	1.667±0.439	1.727±0.486	0.499	>0.05
Age (min)	45.62±25.27	42.62±25.27	50.62±25.27	0.6551	>0.05
Cesarean section	7	9	10	0.20	>0.05
PS use times	1.14±0.47	1.12±0.45	1.30±0.54	1.0344	>0.05
Combined INO treatment	3	4	5	0.21	>0.05
CRRT	1	0	1	10.40	>0.05
Severe NP	19	21	20		
Male	10	9	9	0.42	>0.05
Gestational week	39.26±2.07	39.64±2.57	40.16±2.87	0.6221	>0.05
Birth weight (kg)	2.98±0.77	3.03±0.66	3.18±0.43	0.5321	>0.05
Age (days)	13.91±5.02	14.51±4.92	14.88±4.88	0.1909	>0.05
Maternal infection during delivery	3	1	3	1.50	>0.05
PS use times	1.11±0.32	1.10±0.30	1.40±0.68	2.6675	>0.05
Combined INO treatment	1	1	2	0.54	>0.05
CRRT	1	1	2	0.54	>0.05
MAS	20	21	24		
Male	13	11	12	1.11	>0.05
Gestational week	40.1±1.64	40.9±1.84	41.1±1.24	2.3786	>0.05
Birth weight (kg)	3.951±0.357	3.808±0.355	4.022±0.214	2.7118	>0.05
Age (h)	5.30±1.52	4.41±2.51	5.79±1.95	2.6088	>0.05
PS use times	1.60±0.82	1.62±0.86	1.75±0.90	0.2012	>0.05
Combined INO treatment	3	3	4	0.05	>0.05
CRRT	0	0	0		>0.05

No significant differences were observed between any of the groups. NRDS, newborn respiratory distress syndrome; NP, neonatal pneumonia; MAS, meconium aspiration syndrome; PS, pulmonary surfactant; INO, inhaled nitric oxide; CRRT, continuous renal replacement therapy.

shorter times than the non-lavage group (P<0.05). No statistically significant differences were observed among the three groups as regards air leak, pulmonary hemorrhage, patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), PPHN (P>0.05) (Table II). In addition, no significant differences were found in the OI among the three groups before treatment (P>0.05). Following treatment, the PS lavage group exhibited a more rapid decline in OI than the NS lavage group, and the PS lavage group and NS lavage group exhibited a more rapid decline in OI decline than the non-lavage group, with the differences being statistically significant (P<0.05) (Table III).

Discussion

The age of onset of each disease and diagnostic criteria differ; thus, the inclusion age criteria also differ. The present study examined bronchoalveolar lavage under the ultrasound monitoring of lungs for neonatal atelectasis and lung consolidation. The main subjects of the present study were newborns; thus,

the maximum age was 28 days. NRDS presents as aggravated dyspnea caused by the lack of PS, with an onset time with 12 h, particularly within 6 h. Thus, patients with NRDS are younger than 12 h. MAS is more common in full-term infants or post-term infants. The reason for this is that amniotic fluid mixed with meconium is inhaled while the infant is in the uterus or during delivery, and respiratory distress occurs immediately after birth. Another reason is that the chemical inflammation of lung tissue occurs 12-24 h following meconium inhalation. The presence of lung histochemical inflammation can support the diagnosis of MAS. Thus, patients with MAS are younger than 24 h. Neonatal pneumonia is divided into intrauterine infectious pneumonia, infectious pneumonia during childbirth, and postnatal infectious pneumonia. Therefore, the age of neonatal pneumonia patients is no more than 28 days.

Neonatal atelectasis and lung consolidation diseases are often complicated by severe NRDS, severe NP and MAS, which are common causes of dyspnea, difficulty withdrawing and respiratory failure in newborns. The ultrasound imaging of the lungs can be used to monitor these diseases (1,19,20). Invasive mechanical assisted ventilation is used to ensure that

Table II. Comparison of treatment effects and complications in the three groups.

Group	PS lavage group	NS lavage group	No lavage group	F/χ^2 value	P-value
Severe NRDS	22	24	27		
Lung recruitment time (h)	151.6±63.8	190.4±57.5[a]	226.1±60.9[a,b]	9.1403	<0.05
Invasive ventilator healing period (h)	191.5±57.7	227.8±61.4[a]	261.8±56.6[a,b]	8.7539	<0.05
Air leak	1	1	2	0.31	>0.05
Pulmonary hemorrhage	1	1	4	2.47	>0.05
PDA	8	7	15	3.95	>0.05
BPD	6	6	8	0.14	>0.05
IVH	8	8	12	0.72	>0.05
PVL	7	8	9	0.02	>0.05
Severe NP	19	21	20		
Lung recruitment time (h)	72.0±33.6	97.5±37.5[a]	144.4±35.9[a,b]	20.679	<0.05
Invasive ventilator healing period (h)	91.3±43.7	120.8±41.4[a]	166.7±39.6[a,b]	16.3681	<0.05
Air leak	1	1	2	0.54	>0.05
Pulmonary hemorrhage	1	1	2	3.34	>0.05
MAS	20	21	24		
Lung recruitment time (h)	78.1±29.6	104.5±31.5[a]	151.4±32.1[a,b]	31.5377	<0.05
Invasive ventilator healing period (h)	101.2±28.4	128.7±30.9[a]	179.3±29.8[a,b]	39.4425	<0.05
Air leak	2	2	3	0.14	>0.05
Pulmonary hemorrhage	1	1	1	0.01	>0.05
PPHN	4	4	5	0.03	>0.05

[a]P<0.05, compared with the PS lavage group; [b]P<0.05, compared with the NS lavage group. NRDS, newborn respiratory distress syndrome; NP, neonatal pneumonia; MAS, meconium aspiration syndrome; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; PPHN, persistent pulmonary hypertension of the newborn.

the subject's lung ventilation function is normal, reduce the damage of the oxygen deficit to the body, and withdraw the invasive ventilator after the lungs have re-expanded. Subjects are administered a therapeutic dose of exogenous PS replacement therapy with or no lavage treatment, as severe NRDS, severe NP and MAS can lead to insufficient PS and/or excessive consumption. Exogenous PS replacement therapy can improve lung compliance, stabilize alveolar pressure and can prevent/reduce pulmonary edema. Exogenous PS can also participate in airway immune regulation, which is beneficial to lung disease treatment. Lung ultrasound imaging results have been used to guide whether to use (or reuse) exogenous PS, which can effectively regulate PS application (21-24).

Examination of neonatal atelectasis and lung consolidation diseases with lung ultrasound. The pulmonary ultrasound diagnosis of severe NRDS has a sensitivity of 100% and a specificity of 99%, with no signs of lag on X-ray chest radiographs (19,25). The pulmonary ultrasound diagnosis of NP has a sensitivity of 100% and a specificity of 97.2%, and lung ultrasound imaging can detect changes earlier than other imaging and laboratory tests (9,26). The lung ultrasound diagnosis of MAS has a sensitivity of 90.0% and a specificity of 88.9%. Lung ultrasound has no risk of radiation damage, and can be

examined in real-time, which is more suitable for repeated examination than X-ray chest radiography (2,27).

Pulmonary ultrasound and X-ray chest radiography do not reveal any differences in neonatal atelectasis and the positive rate of lung consolidation (26). Lung ultrasound can be used as a routine and preferred method for such diseases (1,19,25). There are research reports that lung ultrasound can also determine the severity and prognosis of the disease from other information outside the lesion range, such as whether the presence of lung pulsation, and whether there is a CDFI blood flow signal in the lesion area (1,26). Therefore, in the present study, lung ultrasound was used for the diagnosis of severe NRDS, severe NP and MAS, as well as in the follow-up of lung recruitment time, the diagnosis of air leak, pulmonary hemorrhage, etc., which is useful for examinations in real-time. It can also reveal changes in the disease, and may thus help adjust the treatment plan, withdraw the machine in time, clarify the complications and treat them in time, and causes no radioactive damage (1) (Table II).

The ultrasonic equipment manually set the ultrasonic propagation velocity to 1,540 m/sec, and the ultrasonic propagation velocity in the lungs is 440 m/sec. When there is no pleura-pulmonary disease, the ultrasound is totally reflected and lung examination cannot be performed (9). The ultrasound image of the lungs in this case is defined as normal

Table III. Comparison of OI among the three groups of children.

Group	PS lavage group	NS lavage group	No lavage group	F value	P-value
Severe NRDS	22	24	27		
Before treatment	24.9±4.1	24.3±3.9	24.8±3.6	0.1651	>0.05
1 h	14.8±3.7	16.8±3.8	19.2±3.4[a,b]	9.0372	<0.05
12 h	10.3±3.3	13.2±2.8[a]	17.8±2.5[a,b]	43.2587	<0.05
24 h	7.3±2.9	9.5±2.8[a]	14.9±3.6[a,b]	38.5285	<0.05
Severe PN	19	21	20		
Before treatment	25.3±3.7	24.9±3.8	24.7±3.9	0.1253	>0.05
1 h	16.8±3.5	16.7±3.6	19.2±3.4[a,b]	3.2723	<0.05
12 h	11.7±3.1	13.7±2.9[a]	16.8±2.7[a,b]	15.3643	<0.05
24 h	8.1±3.2	10.1±2.7[a]	14.2±3.3[a,b]	20.1629	<0.05
MAS	20	21	24		
Before treatment	26.7±4.4	26.2±4.9	26.9±4.2	0.1412	>0.05
1 h	18.8±3.1	18.3±3.6	21.5±3.4[a,b]	5.9071	<0.05
12 h	12.3±2.4	14.9±2.5[a]	16.7±2.3[a,b]	18.4348	<0.05
24 h	7.8±2.7	10.6±2.6[a]	14.4±3.0[a,b]	31.2314	<0.05

[a]$P<0.05$, compared with the PS lavage group; [b]$P<0.05$, compared with the NS lavage group. NRDS, newborn respiratory distress syndrome; NP, neonatal pneumonia; MAS, meconium aspiration syndrome.

lung features. At this time, the presence of lesions in lung tissue cannot be detected. When pleura-lung disease occurs, for example, atelectasis and lung consolidation, the air in the alveoli is replaced by non-gas material or the alveoli collapses without air, the ultrasonic propagation speed in the diseased area is similar to that in the soft tissue, and can enter the diseased lung area; thus, the examination can be completed. It can be seen that pleura-pulmonary disease is the basis of lung ultrasound examination. Ultrasound can be used for lung examination, however, based on the aforementioned limitations, when the lung ultrasound image is inconsistent with the clinical manifestation, X-ray chest radiography, CT, MRI and other supplementary examinations are required (8,28).

BAL is effective in treating neonatal atelectasis and lung consolidation. The present study demonstrated that BAL was effective in the treatment of neonatal atelectasis and lung consolidation diseases caused by severe NRDS, severe NP and MAS. BAL treatment decreases the time of lung recruitment and invasive ventilator treatment. PS lavage is superior to NS lavage and does not increase complications (Table II). This was consistent with the findings of previous studies (11,12,18). BAL treatment can wash out foreign bodies and secretions in the airway, can unblock the airway, can help improve the hypoxic state and can also promote alveolar recruitment.

During lavage treatment, transcutaneous oxygen saturation (SpO_2) of the child should be >90% (29,30). The analysis of the effects of BAL (29-34) has revealed the following: i) During the lavage process, the uncomfortable stress response of the child stimulates the body through the hypothalamic-pituitary-adrenal axis to produce glucocorticoids, which exert anti-inflammatory effects, conducive to alveolar recruitment; ii) lavage can reduce inflammation and cytokine levels, and can eliminate certain inflammation and cytotoxic factors,

thereby reducing their harm to the body; iii) it can wash out inflammatory exudate, edema fluid, necrotic tissue, etc., which is conducive to alveolar recruitment; iv) lavage fluid from the lavage can be used for smears, stains, and pathogenic examinations to provide a basis for a clear diagnosis and treatment.

BAL treatment can improve OI. The OI is one of the important indicators used to evaluate the effects of respiratory therapy. In the present study, OI was used to evaluate the effect of BAL respiratory therapy in children with severe NRDS, severe NP and MAS (OI = FiO_2 x MAP x 100/PaO_2). It integrates the measured parameters of FiO_2, MAP and arterial oxygen partial pressure (PaO_2), avoiding the limitations of single index evaluation. OI directly reflects the degree of respiratory failure and the respiratory treatment effects in children. It is a commonly used parameter in various countries (35). Normally, the OI is <5. The OI ranges between 10-15 during respiratory insufficiency, with signs of mechanical ventilation and the OI ranges between 15-20 in respiratory failure. When the OI is >25-30, respiratory failure is severe and possibly irreversible; when the OI is >35-40, only extracorporeal membrane oxygenation (ECMO) is generally possible. If the OI increases by 5-10 points within a short period of time, this indicates that the condition has sharply deteriorated, and effective intervention measures must be undertaken immediately. Hypoxic respiratory diseases require active treatment to maintain normal oxygenation, the intracellular oxygenation status cannot be directly monitored, Therefore, OI is used clinically to reflect the oxygenation status of the body of the child (36).

The results of the present study demonstrated that following BAL under ultrasound monitoring, the OI rapidly decreased with the prolonged treatment time, and the PS lavage group exhibited a greater decrease compared with the NS lavage group, indicating that BAL treatment was effective

in improving oxygenation, and was beneficial for improving respiratory function (Table III).

BAL is conducive to unblock the airway; lavage can dilute inflammation and cytotoxic factors, and can lavage out inflammatory exudate, edema fluid, necrotic tissue, etc., which is conducive to alveolar recruitment and clear diagnosis; PS can effectively improve lung compliance and oxygenation, mechanical ventilation can effectively improve ventilation, and the combined application of the three is more effective (20,29,30,32,33).

The present study was prospective study. Severe NRDS, severe NP, and MAS diseases are clinically mainly, dyspnea. The lung ultrasound image reveals atelectasis and lung consolidation. Hence, severe NRDS, severe NP and MAS are considered as a class of imaging diseases. X-ray chest radiographs lead to radioactive damage and these diseases need to be repeatedly monitored. Thus, lung ultrasound technology was innovatively used in real-time in the present study for the dynamic evaluation of whether the lung has been recruited. Moreover, BAL was used in the present study for treatment. In addition to the lung recruitment time and invasive ventilator treatment time, OI is commonly used in international pediatrics, and was also used herein. The aim of the present study was to provide a reference for the clinical application of BAL under the ultrasound monitoring of lungs for the treatment of neonatal atelectasis and lung consolidation diseases. This was a single-center study, and the impact of antibiotics treatment was not evaluated, which poses certain limitations. In the future, the authors aim to conduct a multi-center, large-sample study to also include the impact of antibiotics.

In conclusion, the present study demonstrates that BAL under lung ultrasound monitoring is effective in the treatment of neonatal atelectasis and pulmonary consolidation diseases, that are caused by severe NRDS, severe NP and MAS. It can rapidly decrease the time of neonatal atelectasis, lung consolidation and invasive ventilator treatment, and can also rapidly decrease the OI, without increasing complications. Exogenous PS lavage is also more effective than NS lavage.

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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

FZ conducted the research design, literature review, data collection, data analysis, and manuscript writing. Both authors (FZ and YZ) contributed to the interpretation of the data. YZ participated in data collection. FZ and YZ confirm the authenticity of all the raw data. Both authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Medical Ethics Committee of Dehong Hospital Affiliated to Kunming Medical University (Dehongzhou People's Hospital), China, and informed consent was obtained from the guardians of the children.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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