Mechanical ventilation in clinical management of meconium aspiration syndrome

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Background: Meconium aspiration syndrome (MAS) is frequently seen in term-gestation and post mature infants with severe asphyxia. Mechanical ventilation is currently used in the severe respiratory failure. A retrospective study was undertaken to explore the management of mechanical ventilation so as to reduce the complications and improve the cure rate in the treatment of newborn infants with MAS.

Methods: Sixty-eight patients were divided into groups A, B and C according to the time of admission. Group A, 17 infants, were treated from 1985 to 1989; group B, 25 infants from 1990 to 1995; and group C, 26 infants from 1996 to 2000 by the modified method. In these 3 groups, little difference was seen in the clinical data including sex, gestation, birth weight, and history of abnormal labor. In group C, 26 infants were also complicated by brain injury, 14 by heart failure, 11 by shock, 12 by renal failure, 3 by gastrointestinal dysfunction, and 3 by cardiopulmonary arrest.

Results: The cure rates in groups A, B and C were 23.5%, 60% and 96.2% respectively (H=20.8136, P <0.05, P<0.01). The prognosis rates in the 3 groups were 76.5%, 28% and 3.8%, respectively. The difference between the cure rates and poor prognosis rates among the 3 groups was statistically significant (H=25.55308, χ^2=5.6210, P<0.01, P<0.05). In the three groups, 64.7%, 20% and 7.7% of infants developed pulmonary barotrauma, respectively; 76.5%, 72% and 19.2% infants had acid-base imbalance, and 50%, 25% and 12.5% infants had aggravation of pulmonary infection, respectively.

Conclusions: Strict sterilization and isolation are of utmost importance in mechanical ventilation for the treatment of MAS. The high cure rate of MAS is essential to the prevention of heart, brain, kidney, circulation and gastrointestinal dysfunction in newborn infants. Besides, the improvement of respiratory management as well as the prevention of complications is mostly dependent on the application of mechanical ventilator. According to the conditions of patients and the results of gas analysis, the ventilation parameter was adjusted timely. Improvement of cure rate, prognosis rate, and complications must be associated with the use of mechanical ventilator.

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Key words: mechanical ventilation;
            newborn infants;
            meconium aspiration syndrome;
            complication management

Introduction

Meconium aspiration syndrome (MAS) is a severe respiratory disorder in neonates, for which there is no specific remedy. Approximately 1.2%-1.6% of newborn infants develop MAS involving progressive respiratory distress, hypoxia, hypercapnia and acidosis, and need intensive respiratory therapy. Mortality rates for MAS generally range from 7% to 15.8%.[1] Therefore, it would be of benefit to mitigate the course of this disorder. From 1985 to 2000, we enrolled 68 newborn infants with MAS treated at our NICU, and tried to improve the clinical management.

Methods

Infants

Sixty-eight infants with MAS were divided into 3 groups: A (17 infants), B (25), and C (26). Parents of the infants had provided written informed consent before the trial. Inclusion criteria included diagnosis of MAS and treatment with conventional positive pressure ventilation. MAS was defined as respiratory distress in an infant born through meconium-stained amniotic

fluid with roentgenographic findings consistent with MAS and whose symptoms could not be otherwise explained.[1] The clinical data of the infants in this trial are shown in Tables 1 and 2.

The infants in groups A were enrolled in 1985-1989,[2] group B in 1990-1995,[3] and group C in 1996-2000.[4] Their clinical data showed little difference in demographic characteristics (Tables 1 and 2) ($P>0.05$).

Management

All infants were subjected to oxygen and conventional positive pressure ventilation, treatment of alkalosis and paralysis, and administration of vasopressors or sedatives. The ventilators used in this trial were Babylog type I, Servo 900C, and Bear Cub 750. The infants were confirmed to have type II respiratory failure before the mechanical ventilation. During the ventilation, the blood gas of the infants was kept within 50-80 mmHg of PaO_2 and 35-65 mmHg of $PaCO_2$, and SaO_2 was kept within 85%-95%.

Statistical analysis

All data were shown as mean±SD. An overall effect on a measured variable was evaluated by one-way analysis of variance (ANOVA, the F test). If it was significant, the q test was done for single factor group comparison. In all tests, $P<0.05$ was considered statistically significant. Stat View 5.0 (SAS Institute Inc., USA) was used for the analysis.

Results

The cure rate and poor prognosis rate of group C were significantly higher and lower than those of groups A and B (χ^2=5.4330, 24.6905, 9.8478 and 9.5330, 24.6905, 5.6220, respectively) ($P<0.05$, $P<0.01$) (Table 3). The cure rates in groups A, B and C were 23.5%, 60% and 96.2%, and the poor prognosis rates in the three groups were 76.5%, 28% and 3.8%, respectively.

The incidence of pulmonary barotraumas in groups B and C was significantly lower than that in group A (χ^2=8.4917, 13.2533). The acid-base imbalance in group C was significantly lower than that in groups A and B (χ^2=13.8380, 14.3337). The incidence of infections in group C was lower than that in group A ($P<0.01$, $P<0.05$) (Table 4). In the three groups, 64.7%, 20% and 7.7% of infants developed pulmonary barotraumas, and 76.5%, 72% and 19.2% of infants had acid-base imbalance, respectively. Moreover, 50%, 25% and 12.5% of infants showed aggravation of pulmonary infection.

The parameter of peak inspiratory pressure (PIP) in group A was significantly higher than that in groups B and C (t=3.9843, 5.9685, $P<0.01$). The parameter of positive end expiratory pressure (PEEP) in group C was significantly lower than that in groups A and B (t=6.3455, 3.3224, 2.7317). The parameter in group B was lower than that in group A ($P< 0.01$) (Table 5).

Discussion

MAS is seen frequently in term-gestation infants. In this trial, the outcome of MAS was improved after clinical management including respiratory and ventilation management, circulation and renal support, brain protection, and gastrointestinal nutrition support.[5,6] The comprehensive treatment of MAS increased the cure rate to 96.2% in group C from 23.5% and 60% in groups A and B, respectively (H=20.8136, $P<0.01$).

Table 1. Clinical data of the infants

Group	n	Sex		Gestational age (wk)		Birth weight (g)		Meconium		Abnormal delivery
		Male	Female	≤37	>37	<2500	>2500	II°	III°	
A	17	13	4	1	16	1	16	1	16	9
B	25	18	7	2	23	3	22	2	23	13
C	26	20	6	2	24	2	24	1	25	14
χ^2		0.19089		0.0310*		0.0042*		0.1238*		0.0174

*: H value, $P>0.05$.

Table 2. Complications of the MAS infants in the three groups before ventilation

Group	n	Heart failure	Renal failure	Shock	Gastrointestinal dysfunction	Cardiopulmonary arrest
A	17	8	5	4	1	3
B	25	10	8	7	3	2
C	26	14	12	11	3	3
χ^2		0.9807	1.6253	1.9984	0.2345*	0.1834*

*: H value, $P>0.05$.

Table 3. The outcome characteristics of the infants

Group	n	Cured n (%)	Improved n (%)	Discharged n (%)	Death n (%)	Poor prognosis n (%)
A	17	4 (23.5)	0 (0)	0 (0)	13 (76.5)	13 (76.5)
B	25	15 (60.0)	3 (12.0)	5 (20.0)	2 (8.0)	7 (28.0)
C	26	25 (96.2)	0 (0)	1 (3.8)	0 (0)	1 (3.8)
H value		20.8136	0.1625	0.0010	25.3629	25.55308[*]
P value		<0.01	>0.05	>0.05	<0.01	<0.01

Cure rate (A & B), χ^2=5.4330; poor prognosis (B & C), χ^2=5.6220; P<0.05.

Table 4. Complications of the infants after treatment

Group	n	Barotraumas n (%)	Base-acid imbalance n (%)	Infection n (%)	ICH n (%)
A	17	11 (64.7)	13 (76.5)	6/12 (50)	5/13 (38.5)
B	25	4 (20.0)	18 (72.0)	4/20 (25.0)	9 (36.0)
C	26	2 (7.7)	5 (19.2)	3/24 (12.5)	4 (15.4)
H value		13.1973	14.2748	4.3928	3.5417[*]
P value		<0.01	<0.01	<0.05	>0.05

*: the chi-square test.

Table 5. Ventilation parameters of the infants in the three groups (mean±SD)

Group	n	FiO$_2$ (%)	PIP (cmH$_2$O)	PEEP (cmH$_2$O)	RR (/min)
A	17	0.74±0.17	25.88±2.67	4.53±0.51	63.12±18.18
B	25	0.74±0.15	21±4.53	3.88±0.88	60.4±17.77
C	26	0.685±0.17	19.69±3.61	3.08±0.83	56±22.3
F value		1.0151	14.2167	17.9684	0.69394
P value		>0.05	<0.01	<0.01	>0.05

PIP (cmH$_2$O) A&B, A&C, P<0.01, B&C, P>0.05; PEEP (cmH$_2$O), P<0.01; oxygen flow 6-8 L/min; I/E: 1:1-1:1.2, T1 (s) 0.5-0.6 (FiO$_2$: fraction of inspiratory oxygen; PIP: peak inspiratory pressure; PEEP: positive end expiratory pressure; RR: respiratory rate; I/E: inspiratory/expiratory times ratio).

Strict sterilization and isolation

Strict sterilization is of paramount importance in the course of mechanical ventilation for infants with MAS because of their low defense ability. Since bacterial infection is common in infants receiving mechanical ventilation, we standardized the protocol of sterilization and isolation with special emphasis on the sterilization of ventilation tubes and equipments. Suction tubes were disposable, and the ventilation tube was changed every day. Hand washing was routine before and after management of the infants.[1,5] The infection of *Bacillus klebsiella* was detected in 3 of 91 infants after sputum culture. The infection was controlled by sensitive antibiotics and immune globulins of 400 mg/kg daily. The final infection rates were 50%, 25% and 12.5% in groups A, B and C, respectively.

Management of severe MAS

Respiratory management should fulfill the criteria for clinical treatment of infants with MAS. MAS is usually a complication of placental insufficiency in patients with maternal preeclampsia, hypertension, or post-maturity. In response to stress, the fetus passes meconium and gasps forcefully, thus inhaling meconium mixed with amniotic fluid into the lungs. Severe MAS is often seen in post-term infants with a reduced volume of amniotic fluid because less diluted or thicker meconium is more likely to cause airway obstruction.[6]

Suction is effective before the newborn breathes and cries, resulting in further distribution of meconium through the pulmonary tree.[7,8] After suction, positive pressure ventilation is initiated if depressed respiration is presented. Lavage procedures are necessary in infants with atelectasis.[9,10]

In group B, chest films revealed emphysema in 14 infants and atelectasis in 11. Their average parameters were as follows: PIP (cmH$_2$O) 17.21±1.79, 25.83±1.40; PEEP 3.29±0.61, 4.64±0.50; respiratory rate (RR) 45.43±2.90, 79.45±5.87; fraction of inspiratory oxygen (FiO$_2$) 0.75±0.14, 0.74±0.16; inspiratory/expiratory times ratio (I/E)=1/1.2; and oxygen flow 6-8 L/min. In group C, however, pathological examination showed that the meconium in the airway caused chemical pneumonitis complicated by alveolar atelectasis and emphysema.

Initial ventilation parameters in different infants indicated the severity of respiratory impairment. Oxygenation, chest X-ray features, breath sounds, and respiratory strength were assessed along with arterial or capillary blood gases. Theoretically, X-ray features might be taken as higher parameters of PIP and PEEP during atelectasis but lower parameters of PIP and PEEP during emphysema. In practice, it is very difficult to do so as the patient's conditions change progressively when atelectasis and emphysema in the same lung.[11,12] Pathologically, MAS is characterized by the focal lesions not distributed homogenously in the alveoli of the lung, but scattered normal or nearly normal between the occlusion volume. When sick infants are ventilated, higher pressure and higher tidal volume are needed to make gas flow into the collapsed or occluded alveoli. At the same time, normal alveoli will be over-inflated and gas retention will appear because of poor elastic retraction ability or insufficient expiratory time in occluded alveoli. These factors lead to imbalanced gas homogeneous distribution and mismatch of V/Q ratio. In our study, the PEEP in group C was significantly lower than that in groups A and B. The PIP of group C was significantly lower than that of group A. In the 3 groups, the PIP was 64.7%, 20% and 7.7% respectively for patients with pulmonary barotrauma. The mean airway pressure (MAP) was lower than 12 cmH$_2$O, which shortened the time of a ventilation and reduced the incidence of barotrauma. The high MAP will lead to over-inflation of alveoli, retardation of venous return, decreased cardiac output, and appearance of barotrauma as the oxygenation index is increased. While making the end inspiration lung volume less than total lung volume, the PIP should be lower than 20 mmHg and the PEEP should be kept at 3 mmHg to decrease the incidence of acute lung injury. Synchronized intermittent mandatory ventilation (SIMV) can be used when patients have spontaneous breathes, making weaning from mechanical ventilation easier than IMV mode. To minimize ventilator pressure/volume, which can result in barotrauma with pulmonary air leak or bronchopulmonary dysplasia, permissive hypercarbia is recommended for tolerating an elevated PaCO$_2$ as long as pH remains greater than 7.25. Likewise, PaO$_2$ as low as 60 mmHg is recommended if blood pressure is normal and metabolic acidosis is not present.[13-16]

Prevention of brain edema and brain stem injury

MAS is always complicated by brain injury. The infants in the three groups suffered from hypoxic ischemic encephalopathy (HIE). In groups A, B and C, HIE was mild in 9, 12 and 11 infants; moderate in 5, 9 and 11, and severe in 3, 4 and 4, respectively. Neonatal response to asphyxia follows a predictable pattern that has been demonstrated in a variety of species. When HIE happens, brain blood supply decreases, the blood supply to the right brain decreases because of artery contraction accompanied with disturbance of intra- and extra-cellular anions. These factors lead to brain edema. In our study, 13 infants in group A showed autopsy of brain edema.

Over ventilation may lead to decrease of PCO$_2$, increase of pH value, and respiratory alkalosis. As a result, brain artery contraction and enlargement of end vessels give rise to cerebral ischemia. Moreover, high pressure and long time ventilation can lead to intracranial hemorrhage. A cardinal feature of the defense against hypoxia is the underperfusion of certain tissue beds, e.g., skin, muscle, kidney, and the gastrointestinal tract. Severe MAS is often complicated by HIE. Diffuse hypodensity and loss of differentiation gray/white matter tissues may be shown by early CT, whereas brain atrophy and focal ischemic lesions by later CT. Management of MAS is dependent on supportive care and treatment of specific abnormalities.[10,13,17] In group C of this study, parameters were adjusted according to blood gas and patient conditions. Compared with 76.5% and 72% in groups A and B, acid-base imbalance in group C is reduced to 19.2% (P<0.01). Seizures were treated with intravenous phenobarbital at a loading dose of 20 mg/kg for 24 hours and then at a supportive dose of 5 mg/kg daily for neuroprotective therapy with minimal adverse effects on blood pressure, respiration, or blood gas. In this study, dehydration with furosemide (Lasix) of l mg/kg and opioid receptor antagonist naloxone of 0.05-0.1 mg/kg was prescribed several times daily for the prevention of brain edema and brain stem injury in MAS infants.[17]

Prevention of cardiac, renal and circulatory systems

Circulatory support is extremely important. The control of hypoxia is dependent on the underperfusion of certain tissue beds including skin, muscle, kidney, and the gastrointestinal tract, which allows to maintain perfusion of such principal organs as heart, brain and adrenal glands. When HIE infants are ventilated, intrathoracic pressure is increased, the amount of venous return to the heart decreased, intra-alveoli pressure increased, pulmonary circulation decreased, and right ventricle loading increased with weakened function. Long-time ventilation with higher pressure may lead to decrease of blood pressure and cardiac output. Water retention may be related to increased use of antidiuretic hormone during ventilation. Urine

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amount is decreased significantly when PEEP is used. Thus, attention should be paid to the modulation of ventilator parameters in correcting acid-base imbalance to prevent deterioration of cardiac and renal function.

The dosage of digoxin should be decreased because of the poorly reserved cardiac function. In this study, combined dobutamin and dopamine of 5-10 µg/kg was infused per minute for the correction of cardiac shock, and epinephrine of 0.01-0.03 µg/kg was given per minute to resistant cases. ECG was taken and adrenaline was given until stablization of blood pressure. Dobutamin and phentolamine were given intravenously at 1-20 µg/kg per minute in patients with low output, low resistance cardiac shock. During the treatment, supportive care and treatment of specific abnormalities should be emphasized.[17,18] Fluids should be restricted initially to 60-80 ml/kg daily, oxygenation maintained by mechanical ventilation if necessary, blood pressure supported with judicious volume expansion if it is hypovolemic, and glucose in the normal range of 40-100 mg/dl. Hypocalcemia, coagulation abnormalities, and metabolic acidemia should be corrected. 1,6-FDP is prescribed for the improvement of cardiac nutrition as well as renal circulation.[17-19]

In this study, 2 neonates with persistent pulmonary hypertension were detected in group C. Their treatment included mechanical ventilation with FiO_2 80%-100% and RR 60-90 times per minute since O_2 is a potent pulmonary vasodilator. Alkalinization is also considered to dilate pulmonary arterioles. It is achieved by a slow intravenously infusion of sodium bicarbonate at a dose adjusted by blood gas to keep pH ≥7.45-7.5. Because mechanical expansion of alveoli also causes vasodilation, tolazoline (an α-blocker) given intravenously at a loading dose of 1-2 mg/kg intravenously over 10 minutes and then 1-2 mg/kg per hour may cause pulmonary vasodilation and improve oxygenation. If systemic hypotension develops, systemic hypoxia worsens but can be treated initially with a volume expander, e.g., normal saline or 5% human albumin of 10 ml/kg for over 10 minutes. If blood pressure or perfusion is decreased, the infant could be treated with intravenous dopamine at 5 to 10 µg/kg per minute and/or dobutamine 5 to 10 µg/kg per minute. Often, however, tolazoline-induced hypotension is refractory to treatment, thus limiting the drug's effects. Tolazoline causes histamine release and upper gastrointestinal bleeding. Hence, an H_2 receptor antagonist may be given for prophylaxis.[15]

Finally, it is essential to maintain the gastrointestinal function of patients. In this study, total parenteral nutrition (TPN) (pediatric amino acid fluid 0.5-3 g/kg daily, fat emulsion 0.5-2.5 g/kg daily, glucose 6-12 g/kg daily, electrolyte, vitamin, and microelement) was given to ventilated patients without gastrointestinal feeding, and glucose level was monitored to prevent hypoglycemia and hyperglycemia. We consider that the appropriate dose of glucose is 10-12 g/kg daily. Fat emulsion is maintained by intravenous infusion of 2 g/kg daily for 12 hours to prevent hyperlipemia. Pediatric amino acid is used to decrease the complications of liver injury and cholestasis. One ml of 5% glucose solution is given first, followed by milk 1 ml/kg through a gastric tube with an increasing daily dose if no side-effect exists. When gastric retention appears, feeding is ceased at once. In our study, the median duration of TPN was 6.5 days (4-9 days), hypocalcemia developed in 2 patients, and body weight increased in 14 patients. Strict monitoring should be performed on blood glucose level, blood biochemistry, formation of thrombus, dysfunction of blood coagulation, and cholestasis. According to the conditions of patients, fluid volume can be adjusted from 60 ml/kg to 120 ml/kg, calorie from 50 kcal/kg to 100 kcal/kg daily. Patients with anemia are given blood infusion for early intervention.[20]

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