

# High frequency oscillatory ventilation in meconium aspiration syndrome

Ventilação de alta frequência na síndrome de aspiração meconial

José Nona<sup>1</sup>, Carla Santos<sup>2</sup>, Ana Melo Bento<sup>3</sup>, Cristina Resende<sup>4</sup>, Ana Rodrigues<sup>5</sup>,  
Ana Pinheiro<sup>6</sup>, Odília Nascimento<sup>7</sup>, António Marques Valido<sup>8</sup>

## ABSTRACT

**Objective:** To evaluate and compare the management and associated morbidity in inborn and outborn babies with meconium aspiration syndrome admitted to the Neonatal Intensive Care Unit and ventilated with high frequency oscillatory ventilation. **Methods:** A retrospective cohort study with a review of clinical data from newborns, admitted to the Neonatal Intensive Care Unit during a six-year period (from 1999 to 2004) and ventilated with early high frequency oscillatory ventilation, first intention in inborns and immediately after Neonatal Intensive Care Unit arrival in outborns. **Results:** In the present study, 27 newborns were included: 12 inborn and 15 outborn infants. Severity criteria were similar in both groups. The pulmonary morbidity associated was severe persistent pulmonary hypertension - 12 (seven outborns), pneumothorax - five (three outborns), interstitial emphysema - two (one outborn) and pulmonary hemorrhage - one outborn. Hypoxic-ischemic encephalopathy II-III occurred in six newborns (four outborns). The therapeutic procedures were surfactant administration in 22 newborns (13 outborns), nitric oxide in 12 newborns (7 outborns) and magnesium sulphate in four newborns (three outborns). The median length of ventilation was six days (inborn infants: four and half days; outborn infants: ten days) and the median length of oxygenation supply was ten days (inborn infants: four and half days; outborn infants: 15 days). The median length of stay was 13 days (inborn infants: 11 days; outborn infants: 16 days). One outborn infant died. **Conclusions:** With this ventilation strategy, we have found no significant statistical differences between the two newborn groups, except for the length of oxygenation supply that was longer in the Outborn Group.

**Keywords:** Meconium aspiration syndrome; Infant, newborn; Intensive care, neonatal; High-frequency ventilation; Morbidity

## RESUMO

**Objective:** Avaliar e comparar a atuação e morbidade, associada à síndrome de aspiração meconial, em recém-nascidos na maternidade ou admitidos de fora internados em nossa Unidade de Cuidados Intensivos Neonatal e em ventilação de alta frequência oscilatória. **Métodos:** Estudo retrospectivo, comparativo com revisão dos processos clínicos dos recém-nascidos internados em uma Unidade de Cuidados Intensivos Neonatais durante um período de seis anos (1999 a 2004) e com ventilação de alta frequência oscilatória precoce, de primeira intenção nos nascidos na maternidade e imediatamente após chegada à unidade, nos admitidos de fora. **Resultados:** Neste estudo foram incluídos 27 recém-nascidos, 12 nascidos na maternidade e 15 admitidos de fora. Os critérios de gravidade foram semelhantes em ambos os grupos. A morbidade respiratória associada incluiu hipertensão pulmonar persistente grave - 12 (sete admitidos de fora), pneumotórax - 5 (três admitidos de fora), enfisema intersticial - 2 (um admitido de fora) e hemorragia pulmonar - 1 (admitido de fora). Ocorreu encefalopatia hipóxico-isquêmica graus 2-3 em seis recém-nascidos (quatro admitidos de fora). A terapêutica consiste na administração de surfactante em 22 (13 admitidos de fora), óxido nítrico em 12 (sete admitidos de fora) e sulfato de magnésio em quatro recém-nascidos (três admitidos de fora). A mediana do tempo de ventilação foi de seis dias (4,5 dias para os

*Study carried out at the Department of Pediatrics in the Neonatal Intensive Care Unit of Maternidade Dr. Alfredo da Costa, Lisboa, Portugal.*

<sup>1</sup> Pediatrician at Maternidade Alfredo Costa, Lisboa, Portugal.

<sup>2</sup> Pediatrician at Hospital Cuf Descobertas, Lisboa, Portugal.

<sup>3</sup> Pediatrician at Hospital dos Lusíadas (grupo HPP), Lisboa, Portugal.

<sup>4</sup> Pediatrician at Maternidade Bissaya Barreto, Coimbra, Portugal.

<sup>5</sup> Pediatrician at Hospital Cuf Descobertas, Lisboa, Portugal.

<sup>6</sup> Pediatrician at Hospital do Espírito Santo de Évora, EPE, Évora, Portugal.

<sup>7</sup> Head of Pediatrics Department of Maternidade Dr. Alfredo da Costa, Lisboa, Portugal.

<sup>8</sup> Director of the Pediatrics Department at Maternidade Dr. Alfredo da Costa, Lisboa, Portugal.

Corresponding author: José Nona - Rua Viriato, 1.089-069 - Lisboa, Portugal - Tel.: 351213184029 - e-mail: nonamicha59@gmail.com

Received on Apr 6, 2009 - Accepted on May 14, 2009

The authors received no financing support to conduct this work. All authors declared they participated in preparing the article, are responsible for it and there is no conflict of interest regarding what is stated in the text.

nascidos na maternidade e 10 dias para os admitidos de fora), e a mediana do tempo de suplementação com oxigênio foi de dez dias (4,5 dias para os nascidos na maternidade e 15 dias para os admitidos de fora). A mediana do tempo de internamento foi de 13 dias (11 dias para os nascidos na maternidade e 16 para os admitidos de fora). Um recém-nascido admitido de fora faleceu. **Conclusões:** Com essa estratégia ventilatória, não foram observadas diferenças estatisticamente significativas entre os dois grupos de recém-nascidos, exceto no tempo de necessidade de suplementação com oxigênio, que foi maior no grupo de recém-nascidos admitidos de fora.

**Descritores:** Síndrome de aspiração de mecônio; Recém-nascido; Terapia intensiva neonatal; Ventilação de alta frequência; Morbidade

## INTRODUCTION

Early high frequency oscillatory ventilation (HFOV) in very low birth weight (VLBW) newborns (NB) shows efficacy and seems to be safe<sup>(1-3)</sup>. In NB with birth weight higher than 1,500 g, HFOV is mainly used as a rescue therapy, when all the conventional mechanical ventilation (CMV) strategies fail, but studies about HFOV in the first hours of life in these infants are lacking. Nevertheless, some Neonatal Intensive Care Units (NICU) seem to be successfully using HFOV in meconium aspiration syndrome (MAS).

MAS is an important cause of neonatal morbidity and mortality for which there is no specific therapy or standard approach. Treatments currently used show low efficacy<sup>(4)</sup>.

A comparative study between infants born in our maternity, and outborn infants transferred from other hospitals, initially treated at the hospital of origin and transferred with an expert team of Intensive Neonatal Care, was only possible due to statistically similar demographic data, severity index, time of ventilation start and surfactant administration.

## OBJETIVO

The purpose of this study was to evaluate the results of HFOV initiated in the first hours of life in NB with MAS (inborn and outborn babies). It was analyzed the outcomes until hospital discharge, mainly by evaluation of three parameters: ventilation and oxygenation time, morbidity (respiratory and others) and mortality.

## METHODS

A retrospective cohort study, with a review of clinical data from NB admitted to a NICU during a period of six years (January 1<sup>st</sup>, 1999 to December 31<sup>st</sup>, 2004). Inclusion criteria included admission to NICU in this period of time, MAS diagnosis and mechanical

ventilation with HFOV in the first hours of life. Twenty-seven neonates met the criteria.

HFOV in inborn infants was a first intention method, the only and exclusive ventilation mode, initiated immediately after intubation in the NICU or after NICU arrival from the delivery room. In outborns, it began immediately after arrival at the NICU.

In this ventilation strategy, an initial mean airway pressure (MAP) between 12 and 15 cm H<sub>2</sub>O was used, accordingly with its clinical status, in inborn infants, and a MAP 1 to 2 cm H<sub>2</sub>O above the corresponding pressure used in CMV, in the outborn infants. Initial FiO<sub>2</sub> was 100% or less, related with clinical severity of the underlying persistent pulmonary hypertension (PPH).

Concerning surfactant therapy, beractant (Survanta<sup>®</sup>) was administered in 4 ml/kg (100 mg/kg) doses, instilled gently through a closed airway circuit system, as soon as possible. If necessary, additional doses were given no sooner than six hours later. Administration criteria were a MAP *versus* FiO<sub>2</sub> higher than three to four, and a/A O<sub>2</sub> below 0.22-0.17. In surfactant lavage, a dilution with a 6 mg/ml phospholipidic concentration was used, with the total administered dose equivalent to 10 to 15 ml/kg of the dilution, divided into four or five aliquots.

Once the following criteria were met: MAP ≤ 8.0 – 9.0 cm H<sub>2</sub>O; fraction of inspired oxygen (FiO<sub>2</sub>) ≤ 30% and the baby breathing spontaneously and regularly on HFOV without any signs of respiratory distress, extubation was performed and followed by nasal continuous positive airway pressure (NCPAP) or supplemental oxygen in the incubator.

Oxygenation index (OI) was defined as the worst one in the first six hours of life, always before surfactant administration, in the inborns, or in the first six hours after admission in the NICU (before surfactant administration or readministration) in the outborns.

Statistical analysis was performed using Mann-Whitney test for continuous variables, which were birth weight (BW), gestational age (GA), ventilation time, oxygen supplementation time and length of stay, and  $\chi^2$  or Fisher's exact test for categorical variables. Odds ratio and 95% confidence intervals (CI) were calculated for the results concerning NB clinical course.

## Sample characterization

Of the 27 NB included in this study, 12 were inborns (44%) and 15 outborns (56%), with a median of six hours of life upon NICU admission.

The identified risk factors, with anomalies in the fetal cardiotocogram (CTG) being the most important, are represented in Table 1.

**Table 1.** Identified risk factors including anomalies in the fetal cardiocotogram

Risk factors	Number	Inborn/outborn
CTG anomalies	11	6 / 5
Maternal disease	4	3 / 1
Small for gestational age	3	0 / 3
Chorioamnionitis	5	4 / 1
Post-term delivery	2	0 / 2
Ruptured membrane > 24 h	4	2 / 2

CTG: cardiocotogram.

Fifteen NB were male (six inborns and nine outborns) and 12 female (six inborns and six outborns), the median GA was 40 weeks, for inborns, and 39 weeks for outborns, and median BW was 3,522 g in inborn infants and 3,210 g in outborn infants. Normal delivery was observed in 12 NB (five inborns and seven outborns). The remaining infants, distocic childbirths, were born by cesarean section (six inborns and seven outborns), vacuum (one inborn) or forceps (one outborn) delivery.

Median five-minute Apgar Score was seven in both groups of NB. Severity index, SNAPE II and OI showed median values of 35/18 for inborns and 39/23 for outborns.

Inborns were ventilated within a median time of 60 minutes, and outborns, 90 minutes. Median time of surfactant administration (first dose) and surfactant lavage was 90 minutes in the inborns and 120 minutes in the outborns. In both groups, the median number of doses administered was identical (two doses), as seen in Table 2.

**Table 2.** Evaluation of the time to initiate ventilation and surfactant administration in two groups (inborn/outborn)

Time to initiate ventilation and surfactant administration	Inborn (n = 12) Median	Outborn (n = 15) Median
Time to initiate ventilation	1 h	1 h 30 minutes
Time of surfactant administration (1 <sup>st</sup> dose)	1 h 30 minutes	2 h
Time of surfactant lavage	1 h 30 minutes	2 h
Surfactant doses	2	2

## RESULTS

Surfactant was administered in 17 NB (63%, seven inborns and ten outborns), and surfactant lavage was made in five (18.5%, two inborns and three outborns).

The assisted ventilation device used in all NB enrolled in this study was SensorMedics (SensorMedics 3100A™, SensorMedics Corp., Yorba Linda, CA). Median lengths of ventilation and of oxygen supplementation were six and ten days, respectively. Statistical analysis of data between the two groups concerning oxygen supplementation showed a significant difference, with a longer total time in the outborns (15 days in outborns *versus* four and half days

in inborns). We also found a higher median ventilation time/length in outborns, but this difference was not statistically significant (Table 3).

**Table 3.** Ventilation time and length of oxygen supply

Ventilation time and length of oxygen supply	Total Median [min - max]	Inborn/outborn Median	Odds Ratio [95%CI] Cut-off = 9.5 days
Ventilation time	6 days [1 - 16 days]	4.5 / 10.0 days	OR = 0.22 [0.03 - 1.5]
Length of O <sub>2</sub> supply	10 days [2 - 60 days]	4.5 / 15.0 days	OR = 0.12 [0.01 - 0.89]

After extubation, nine infants (33%, four inborns and five outborns) started receiving NCPAP. In the other, 18 infants (67%, 11 inborns and seven outborns) only oxygen supplementation was administered.

Associated respiratory morbidity recorded in this study was: severe PPH in 12 NB (44.4%), pneumothorax in 5 (18.5%), pulmonary interstitial emphysema in 2 (7.4%) and pulmonary hemorrhage in 1 (3.7%). Statistical analysis of the incidence of severe PPH and pneumothorax between the two groups was performed, but no statistically significant differences were found (Table 4).

**Table 4.** Associated respiratory morbidity recorded in this study

Associated respiratory morbidity	Inborn/outborn	Odds Ratio [95%CI]
Persistent pulmonary hypertension	5 / 7	OR = 0.82 [0.14 - 4.91]
Pneumothorax	2 / 3	OR = 2.17 [0.22 - 24.1]
Pulmonary interstitial emphysema	1 / 1	-
Pulmonary hemorrhage	0 / 1	-

Hypoxic-ischemic encephalopathy (HIE) II-III occurred in six (22%) of the 27 NB, two inborns and four outborns (OR = 0.55; 95%CI = 0.05-4.87). Imaging study (transfontanelle ultrasonography, computerized tomography, nuclear magnetic resonance) showed ischemic stroke in two cases (one inborn and one outborn), basal ganglia hemorrhage in one outborn and hemorrhagic parenchymal infarction in another outborn infant.

Inhaled nitric oxide (INO) therapy was necessary in 12 (44.4%) NB, five inborns and seven outborns (OR = 0.82; 95%CI = 0.13-4.91) and magnesium sulphate in four (14.8%) NB, one inborn and three outborns.

The median length of stay was 13 days, a minimum of six and a maximum of 39 days, 11 in the inborns and 16 in the outborns (OR = 0.44; 95%CI = 0.07-2.71). One of the outborn infants died in the eighth day of life due to HIE III.

## DISCUSSION

In regard to the demographic data of the study population, we would like to point out that both groups, inborn and outborn, showed similar characteristics, with a median GA of 40 weeks and a median BW of 3,350 g. Clinical severity was also equivalent, according to the severity index, OI and SNAPPE II<sup>(6)</sup>. Both groups underwent similar therapeutic procedures.

Surfactant administration has been showing efficacy with improved oxygenation and ventilation (decreasing ventilation length) in NB with MAS<sup>(6-9)</sup>. This was seen in this study as surfactant was used in most (63%) of the infants. Some authors have reported clinical improvement with lung surfactant lavage<sup>(10-11)</sup>, but this is still controversial, which justified the use of this approach in five cases (two inborn) only.

INO associated to HFOV seems to be an effective therapeutic agent, with oxygenation refinement<sup>(12)</sup>, especially in NB with MAS associated PPH<sup>(13)</sup>, decreasing extracorporeal membrane oxygenation (ECMO) needs. INO was used in the 12 cases of severe PPH described, with a good outcome in terms of OI.

Total ventilation and the times of oxygen supplementation found in this study, with a median of six and ten days respectively, were similar to those found in other studies of NB with MAS<sup>(4,7,14)</sup>. In the meanwhile, when we compared inborns and outborns, it was found a higher ventilation time in outborns (median time of 10 days *versus* four and half days in inborns), but not statistically significant, and a longer oxygen supplementation time was also seen in outborns (median time of 15 days *versus* 4.5 days in inborns), with  $p = 0.0063$  considered statistically significant.

When it was evaluated respiratory morbidity in the NB, major complications and the usual survival status were severe PPH (12 cases, 63%) and pneumothorax (5 cases, 15%), described in the literature as the main respiratory problems associated with MAS; both groups showed similar results.

HIE II-III was diagnosed in six NB (22%), presumably related to clinical severity, with a slightly higher incidence in outborns (four outborns *versus* two inborns).

Length of hospital stay was longer in outborns (16 *versus* 11 days), but not statistically significant. Mortality rate was 3.7% (one NB), which resembles previous reports of MAS<sup>(15-16)</sup>.

## CONCLUSIONS

Considering previous experiences in the treatment of these NB with CMV, we believe that with this therapeutic

strategy, mainly with the ventilation approach, good results in terms of associated morbidity and mortality were achieved.

Some differences were observed in the clinical course of the outborn infants when compared to inborn infants, which seems to reinforce the major relevance of early initiation of this therapeutic and ventilation strategy to achieve success.

Despite all the efforts, we realized that this study has its limitations, mainly due to the small population size that did not allow statistically significant conclusions. We consider that the need to carry out randomized prospective studies to evaluate the efficiency and effectiveness of this ventilation strategy in this specific population is of major relevance.

## REFERENCES

- Rimensberger PC, Beghetti M, Hanquinet S, Berner M. First intention high-frequency oscillation with early lung volume optimization improves pulmonary outcome in very low birth weight infants with respiratory distress syndrome. *Pediatrics*. 2000;105(6):1202-8.
- Nona J, Nogueira M, Nascimento O, Costa T, Valido AM. Ventilação de alta frequência oscilatória exclusiva com otimização do volume pulmonar no recém-nascido de extremo baixo peso: estudo comparativo com ventilação de alta frequência oscilatória após ventilação convencional. *Acta Pediatr Port*. 2001;32(4):225-31.
- Nona J, Nogueira M, Nascimento O, Costa T, Valido AM. Ventilação de alta frequência oscilatória como método ventilatório único e exclusivo e com estratégia de otimização do volume pulmonar no recém-nascido de muito baixo peso. *Acta Pediatr Port*. 2003;34(5):345-52.
- Wiswell TE, Knight GR, Finer NN, Donn SM, Desai H, Walsh WF, et al. A multicenter, randomized, controlled trial comparing Surfaxin (Lucinactant) lavage with standard care for treatment of meconium aspiration syndrome. *Pediatrics*. 2002;109(6):1081-7.
- Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: simplified newborn illness severity and mortality risk scores. *J Pediatr*. 2001;138(1):92-100.
- Findlay RD, Taeusch HW, Walther FJ. Surfactant replacement therapy for meconium aspiration syndrome. *Pediatrics*. 1996;97(1):48-52.
- Soll RF, Dargaville P. Surfactant for meconium aspiration syndrome in full term infants. *Cochrane Database Syst Rev*. 2000;(2):CD002054.
- Auten RL, Notter RH, Kendig JW, Davis JM, Shapiro DL. Surfactant treatment of full-term newborns with respiratory failure. *Pediatrics*. 1991;87(1):101-7.
- Khammash H, Perlman M, Wojtulewicz J, Dunn M. Surfactant therapy in full-term neonates with severe respiratory failure. *Pediatrics*. 1993;92(1):135-9.
- Gelfand SL, Fanaroff JM, Walsh MC. Meconium stained fluid: approach to the mother and the baby. *Pediatr Clin North Am*. 2004;51(3):655-67.
- Lam BC, Yeung CY. Surfactant lavage for meconium aspiration syndrome: a pilot study. *Pediatrics*. 1999;103(5 Pt 1):1014-8.
- Rais-Bahrami K, Rivera O, Seale WR, Short BL. Effect of nitric oxide and high-frequency oscillatory ventilation in meconium aspiration syndrome. *Pediatr Crit Care Med*. 2000;1(2):166-9.
- Wiswell TE. Advances in the treatment of the meconium aspiration syndrome. *Acta Paediatr Suppl*. 2001;90(436):28-30.

14. Salvia-Roigés MD, Carbonell-Estrany X, Figueras-Aloy J, Rodríguez-Miguélez JM. Efficacy of three treatment schedules in severe meconium aspiration syndrome. *Acta Paediatr.* 2004;93(1):60-5.
15. Nolent P, Hallalel F, Chevalier JY, Flamant C, Renolleau S. Meconium aspiration syndrome requiring mechanical ventilation: incidence and respiratory management in France (2000-2001). *Arch Pediatr.* 2004;11(5):417-22.
16. Cleary GM, Wiswell TE. Meconium-stained amniotic fluid and the meconium aspiration syndrome: an update. *Pediatr Clin North Am.* 1998;45(3):511-29.