ORIGINAL ARTICLE

Respiratory distress due to surfactant deficiency in a third-level hospital with no in-patient deliveries: mortality-related factors

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Abstract

Background. Surfactant deficiency is a frequent cause of respiratory distress in the preterm newborn. The aim of this study is to determine the factors associated with mortality.

Methods. We studied 257 cases in a tertiary-care neonatal intensive care unit with no in-hospital deliveries. We compared survivors and deaths with the χ^2 test and calculated odds ratio and 95% confidence interval. We subdivided the cases at 1500 g searching for any differences.

Results. Of the newborns, 60% were male. Mean birth weight was 1 666 g and gestational age was 31 weeks. In only 9% was there pulmonary maturation induction with steroids. Overall mortality was 30%. Statistical differences were found between live newborns and deaths according to mean birth weight (1 812 g *vs.* 1321 g, p <0.001) and gestational age (32 *vs.* 29 weeks, p <0.001). Associated risk factors were maternal diabetes (OR 9.8, 95% CI: 1-89) and threatened abortion (OR 13.2; 95% CI: 2.8-62). There was no difference between those babies who received or did not receive surfactant or whether it was received before or after 3, 6 or 12 h.

Conclusions. Mortality due to surfactant deficiency was high, especially among lower birth weight infants. Surfactant did not lower mortality in this group.

Key words: newborn, preterm, respiratory distress syndrome, hyaline membrane disease, surfactant.

Introduction

Surfactant deficiency is manifested by respiratory distress that begins shortly after birth and progresses over the next 72 h.[1] Radiographic images are typical for pulmonary hypoventilation (with six or seven intercostal spaces), generalized radiopacity (described as ground glass or unpolished image), air bronchogram and other fine reticular and granular images.[2] Blood gases initially show hypoxemia and hypercapnia and rapidly mixed acidosis is added. The cause is the decrease in the quantity and/or quality of natural surfactant factor produced by type II pneumocytes, mainly secondary to the immaturity of pre-term newborns.[1,3,4] The condition is also referred to as hyaline membrane disease (HMD), multiple microatelectasias syndrome, respiratory distress syndrome (RDS) and often just referred to in the literature simply as RDS although to refer to it as such does not allow distinction from other causes of neonatal respiratory distress. Surfactant deficien-

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Fecha de recepción: 19-08-09
Fecha de aceptación: 12-01-10

cy allows for a great superficial tension in air-fluid interface in the alveoli, leading to a low lung compliance and alveolar collapse, generating great difficulty in breathing. Alveolar hypoventilation and hypoxemia lead to tissue hypoxia with an increase in anaerobic glycolysis and metabolic acidosis.[6,7] Hyaline membranes are a histopathological finding and consist of damaged epithelium and alveolar eosinophilic proteinaceous exudate generated by increased capillary permeability and edema, particularly in one lung-assisted ventilation.[5]

HMD presents itself in 24 000 patients annually in the U.S.[5] Factors have been described that increase the incidence and severity such as maternal diabetes,[8,9] masculine gender[5,10] and birth via cesarean section without labor. Factors that decrease its incidence are hypertensive disorders of pregnancy, premature rupture of membranes, narcotic addiction, smoking and, importantly, exposure to steroids shortly before preterm birth.[9,11] There may be surfactant decrease due to lack of synthesis or by inactivation secondary to asphyxia, hypothermia, pneumonia, meconium or pulmonary hemorrhage.[12] Mortality has been historically high, being one of the reasons that limits viability. From the use of exogenous surfactant in the early 1990s, a decrease in mortality >50% was reported.[13]

The present study was conducted with the objective of determining the factors associated with mortality in patients with HMD during the last 15 years in a tertiary-care hospital without maternity facilities. Patients were transferred from second-level public hospitals and private institutions in the metropolitan area of Mexico City and nearby cities.

Patients and methods

We conducted a retrospective, cross-sectional, observational and analytical investigation corresponding to a case series. Medical records were searched for a list of patients with diagnosis upon admission of "newborn respiratory distress" and, specifically, "hyaline membrane disease of the newborn" with code CIE X P22.0[14] from January 1, 1993 to December 31, 2008. The list was supplemented with the log of admissions and discharges from the Department of Neonatology and the electronic statistics of the department itself. Clinical records were located and confirmed that the clinical and radiological diagnostic criteria were met, according to notes in the medical record. Cases with respiratory distress in the first hours of life and x-ray reporting bilateral homogeneous opacity with air bronchogram without any other obvious cause of respiratory distress such as pneumonia, aspiration syndrome, or air leak at time of diagnosis were considered compatible for HMD. At this time, the patient was included as a case and the following data were extracted from the clinical records: demographic data, maternal and perinatal history, use of surfactant and, if necessary, number of dosages and age at the first application, concomitant diseases, sequelae and reason for discharge. Some missing values were managed as follows: in three cases birth weight was unknown and was scored at the 50th percentile for gestational age. In the dichotomous variables, proportions were calculated based on available data without recoding missing values. In six variables there were one or two missing values and there were seven cases of hyperbilirubinemia with missing values. We considered that these missing values did not change the trend in the variables. Apgar score was not included because these data were unknown in 32 patients at the time of evaluation and in 35 patients at 5 min. In the case of surfactant, of 72 cases that met the criteria, only in 52 cases is the age of application of the first dose known. Remaining cases were excluded from analysis due to time of the initial dose.

The sample was divided into survivors and those who died. χ^2 test or Fisher exact test was used to determine differences among groups. For variables expressed as proportions, odds ratio (OR) and 95% confidence interval was calculated. It was considered significant when the confidence interval did not include the unit. For continuous variables, mean, standard deviation and differences between the means were calculated. Levene test for homoge-

neity between variances was performed first and then the appropriate Student t-test was applied. Two-tailed á values were calculated; $p < 0.05$ was accepted as statistically significant.[15]

The sample was subsequently divided into two subgroups: one with weight <1 500 g and the second with weight ≥1 500 g. Independent variables were compared for maternal and perinatal history. χ^2 test or Fisher exact test was done to observe differences in mortality between subgroups. OR and 95% confidence interval were calculated.[15] The study was approved by the institutional research committee.

Results

We included 257 patients from January 1993 to December 2008. Average gestational age was 31.4 weeks (SD 3.1) and median was 32 weeks with a range of 24-38 weeks. Age at admission was on average 29 h (SD 61 h) with values ranging from 0-648 h. Average weight was 1 666 g (SD 571 g) with a median of 1 650 g with values ranging between 600 and 3 760 g. Of the patients, 59.5% (153 patients) were males ($p = 0.002$). The most frequent maternal history is shown in Figure 1. In 97 patients (37.7%) there was fetal distress, in five patients (1.9%) there was prolonged rupture of membranes and 145 patients (56.4%) were born via cesarean section. In only 23 cases (8.9%) was there induction of lung maturity due to maternal steroid application.

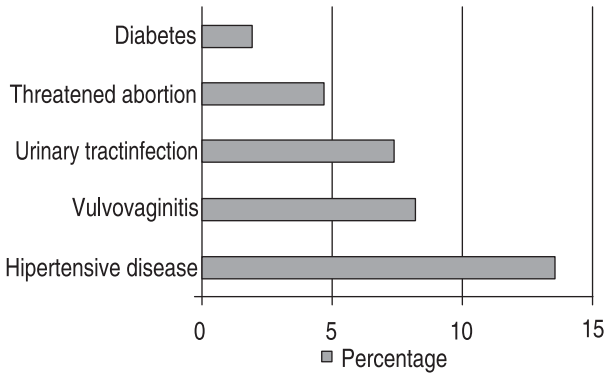

Figure 1. Most frequent maternal history in the series. Respiratory difficulties due to surfactant deficiency in the Instituto Nacional de Pediatría (INP) (1993-2008).

Onset of respiratory distress in 54.5% of cases was at birth. Two hundred thirty two patients required mechanical ventilation (90%) with an average duration of 9.9 days (SD 7.4 days) and median of 6 days. Surfactant was administered to 72 patients (28%) in the hospital of origin or the referral hospital. In 52 patients, the age at first application was known. Among those known, the average age of application of the initial dose was 16 h with a median of 8 h (0-72 h). In 22 patients the application was prior to 6 h and 24 patients received the first dose after 12 h.

Associated diseases are seen in Figure 2. The most frequently associated treatments were antibiotics (96.1%), transfusions (69.6%), methylxanthines (54.5%), indomethacin (49.8%) and parenteral nutrition (46.3%). Thirty four patients (13.2%) required surgical closure of the ductus arteriosus and 31 patients (12.1%) required exchange transfusion. Onset of respiratory distress in 54.5% of cases was at birth. Two hundred thirty two patients required mechanical ventilation (90%) with an average duration of 9.9 days (SD 7.4 days) and median of 6 days. Surfactant was administered to 72 patients (28%) in the hospital of origin or referral hospital. In 52 cases the age at first application was known, among which the average age of application of the initial dose was 16 h with a median of 8 h (0-72 h); for 22 patients it was applied prior to 6 h after admission and 24 patients received the first dose after 12 h.

Average hospital stay was 25 days (SD 23 days) with a median of 19 days. Sequelae were detected in 101 patients (39.3%). There were 63 cases (24.5%) with bronchopulmonary dysplasia, 49 cases (19.1%) with psychomotor retardation, and two cases (0.8%) with retinopathy. Some patients had more than one type of sequelae and 77 patients died (29.9%).

Mortality within each weight group is shown in Table 1. Tables 2 and 3 show some variables where

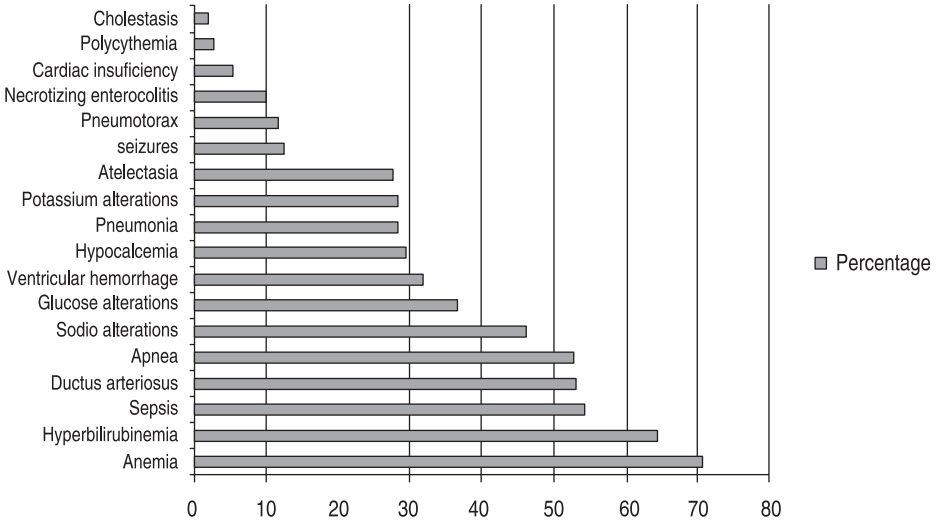

Figure 2. Associated diseases conditioned by prematurity. Respiratory difficulties due to surfactant deficiency in INP (1993-2008).

Table 1. Mortality due to respiratory difficulty because of surfactant deficiency according to weight group (INP 1993-2008)

Weight group (g)	Cases	Deaths	% mortality
500-749	8	6	75
750-999	18	13	72
1000-1249	43	21	49
1250-1499	34	14	41
1500-1749	39	11	28
1750-1999	40	5	13
2000-2249	34	3	9
2250-2499	17	0	0
2500-2749	13	2	15
2750-2999	8	1	13
3000 and higher	2	1	50

INP, Instituto Nacional de Pediatría.

Table 2. Differences between survivors and deaths due to respiratory difficulty because of surfactant deficiency (INP 1993-2008)

Variable	Survivors	Deaths	*p* value
Gestational age (weeks)*	32	29	0.000
Birth weight (g)*	1812	1321	0.000
Age at initiation (h)	2.8	6	0.004

INP, Instituto Nacional de Pediatría.

there was significant difference between survivors and those patients who died. There was no significant difference in mortality with male patients. There was also no significant difference if antenatal steroid was used. Table 4 shows the mortality with the use of surfactant at different times. Data were not significant. Figure 3 shows the trend in mortality rate during the last decade.

By subdividing the series according to weight for those <1 500 g, significance was obtained for history of threatened abortion in the first quarter with 0% of patients alive and 100% died ($p = 0.006$, Fisher), OR 0.471 (95% CI 0.383-0.578). For surfactant variable, after 12 h there was only a trend toward significance ($p = 0.09$), OR 6.41 (95% CI 0.99-41).

For neonates >1500 g, the variable for diabetes was significant with 33% of survivors and 66% of deaths ($p = 0.54$, Fisher) and OR 0.198 (95% CI 0.08-0.48). For the variable of cesarean delivery, 89.9% survived and 10.1% died ($p = 0.037$) and OR of 0.378 (95% CI 0.148-0.966).

Discussion

Patients treated for RDS secondary to surfactant deficiency show a wide variation in gestational age only 10.9% were immature (<28 weeks). The institution where the study was conducted has no births.

All patients are referred for interhospital transfer. The most immature infants are often too unstable to move and many of them die early, before being transferred to a tertiary-care center. In a maternity hospital, one would expect a higher proportion of immature infants. In addition, 4.7% infants were at term, suggesting that some patients had the disease due to use of surfactant rather than immaturity. As has been reported in the literature, in this sample male gender also predominated with significant difference.[16-18]

Regarding maternal diseases, a higher incidence of surfactant deficiency has been reported in diabetic mothers, but in this sample it was observed in <5%. In contrast, it was mentioned that hypertensive disorders of pregnancy promote lung maturation. In the sample this was found as the most frequent antecedent. One explanation would be that in the face of a hypertensive crisis it is necessary to terminate the pregnancy even though it has not reached term because maturity would be relative.

Although the usefulness of maternal steroids to promote fetal lung maturity has been demonstrated,[19] it was only used in 8.9% of cases. International studies report its use in ~80% of pregnancies >24 weeks.[13] Jonguitud et al. found steroid use in 8% of late preterms who had respiratory difficulty.[20] In Mexico, little progress has been made in this regard. Fifteen years ago we published that in only 5.2% of cases of respiratory distress due to

Table 3. Factors associated with mortality due to respiratory difficulty because of surfactant deficiency (INP 1993-2008)

Variable	Deaths	Survivors	OR	95% CI	*p**
Diabetes	4/5 (80%)	1/5 (20%)	9.8	1 - 89	0.029**
Threatened abortion	10/12 (83%)	2/12 (17%)	13.3	2.8 - 62	<0.001
Cesarean delivery	29/145 (20%)	116/145 (80%)	0.33	0.19 - 0.58	<0.001
Apnea	25/136 (18%)	111/136 (82%)	0.3	0.17 - 0.53	<0.001
PDA	24/137 (17%)	113/137 (83%)	0.27	0.15 - 0.47	<0.001
Pneumonia	14/73 (19%)	59/73 (81%)	0.46	0.24 - 0.88	0.017
Atelectasis	7/71 (10%)	64/71 (90%)	0.18	0.08 - 0.42	<0.001
Indomethacin	20/128 (16%)	108/128 (84%)	0.23	0.13 - 0.42	<0.001
Theophylline	22/140 (16%)	118/140 (84%)	0.21	0.12 - 0.38	<0.001
Ligation of conductus arteriosos	2/34 (6%)	32/34 (94%)	0.12	0.03 - 0.53	< 0.001
Parenteral nutrition	27/118 (23%)	91/118 (77%)	0.53	0.3 - 0.92	0.02

*χ^2 test.
**Fisher exact test.
OR, odds ratio; CI, confidence interval; PDA, patent ductus arteriosus; INP, Instituto Nacional de Pediatría.

Table 4. Mortality due to respiratory difficulty because of surfactant deficiency comparing application or no application of surfactant at different time points (INP 1993-2008)

Comparison groups	% Mortality	*p* Value*	Risk	95% CI
No surfactant *vs.* surfactant	32.4 *vs.* 23.6	0.166	0.644	0.345–1.20
Surfactant <3 *vs.* >3 h	25.0 *vs.* 33.3	0.747	0.667	0.177–2.51
Surfactant <6 *vs.* >6 h	31.8 *vs.* 34.4	0.845	0.891	0.280–2.80
Surfactant <12 *vs.* >12 h	28.6 *vs.* 33.3	0.711	1.25	0.384–4.06
No surfactant *vs.* >12 h	32.4 *vs.* 34.8	0.821	1.11	0.447–2.70

*χ^2 test.
CI, confidence interval; INP, Instituto Nacional de Pediatría.

surfactant deficiency would pulmonary maturity be induced,[16] and 10 years ago in a hospital that cares for high-risk pregnancies 16.6% of cases of lung maturity induction with antenatal steroids was reported.[21] Only one publication of a hospital in Mexico mentions 39% of cases with this history.[22] The recommended scheme is with betamethasone (12 mg IM/24 h for two doses).[1]

The most frequently associated pathological condition was anemia. In addition to anemia of prematurity, surfactant-deficient patients have a prolonged hospital stay (in this study up to 149 days) and require blood samples for diagnostic tests and metabolic control. A previous study showed that premature babies have up to 20.5% of blood volume extracted for this reason.[23] Other associated diseases were found to reflect the lack of maturity in multiple organ systems, typical of premature babies.

Of the 180 survivors, 56.1% had some sequelae. Locally, it implies a better outcome with respect to a previous study that found that 72% of patients presented with sequelae.[16] It has been reported that comprehensive treatment in the cases of surfactant deficiency has improved survival with and without sequelae.[24] Engle, in a review of surfactant, mentions that it increases survival without altering the incidence of neurosensory disability and development.[12] The most frequent sequelae was bronchopulmonary dysplasia (35% of survivors) as a result of ventilatory management, necessary in cases of respiratory distress due to surfactant deficiency and almost equal to 37.7% from the previous study. It is known that most lung damage results from assisted ventilation, especially when there is a need for high parameters or prolonged ventilation. This interpretation is supported by the results of 89 patients with assisted mechanical ventilation for >10 days. The lung is not damaged at birth[25] even when there is pulmonary sequestration in a premature patient. Classic hyaline membranes are not formed in the sequestered lobe but are formed in the lung communicated by the airway.[26]

Regarding neurological sequelae, these were detected in 19.1% of cases at discharge in this series. This meant a reduction in the institution to less than a third of the 62.3% found in the previous study. Fernandez-Carrocera et al.[27] reported about 50% of neurological deficit at 1 year of follow-up, but their population had lower birth weight and lower gestational age and therefore increased risk.

Mortality of ~30% is very high when compared with that present in developed countries.[13] In Mexico, in the era of surfactant, mortality ~50% was reported by Sanchez-Mendiola et al. at the Central Military Hospital,[18] 41.5% by Perez-Molina et al.,[17] 29% by Salinas et al. in the National Institute of Perinatology.[21] Morilla et al. reported a mortality of about 10% in Cuba[28] and Lopez-Anacleto et al. of 9.8% in the Belisario Domínguez Specialty Hospital in Mexico City.[22] However, the population of the latter is different because all patients were treated with surfactant. The ratio of induction of lung maturity was four times higher than our cases and at least 30% of patients had a grade I HMD.

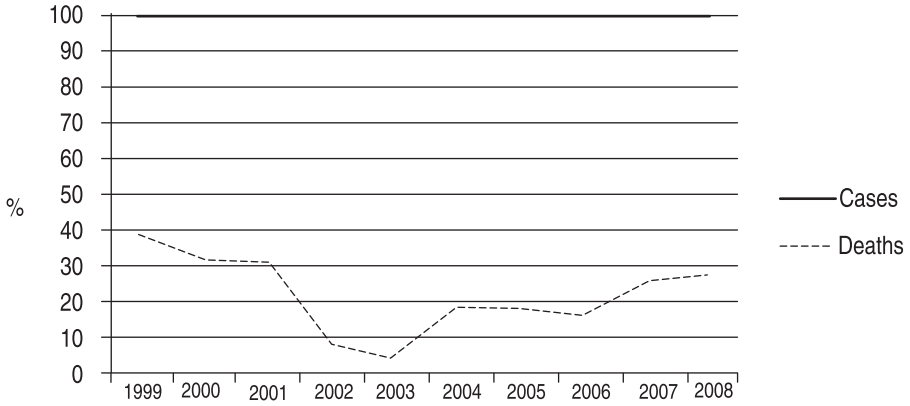

Figure 3. Relative mortality in the last decade. Respiratory difficulties due to surfactant deficiency in INP (1999-2008).

Although higher mortality has been reported in males, in our sample there was no significant difference according to gender.

It is easy to explain why, in the group who died, weight and gestational age were lower because the greater the immaturity, the more serious the disease due to surfactant deficiency as well as structural immaturity. The lung is in saccular or even canalicular phase[29] and the response to exogenous surfactant is less.[25] Diabetes mellitus has been a factor associated with poor development in patients with HMD. We found this in the complete series and in the subgroup of >500 g. Diseases shown in Table 2 are explained in greater frequency among the survivors, not because they are a protective factor for mortality but because the survivors have had sufficient time (average hospital stay 32 days) and exposure to various factors in their evolution. On the other hand, the group who did not survive died at an average of 8 days; therefore, they did not develop other diseases at the same frequency.

Usefulness of surfactant as prophylactic and in early rescue has been sufficiently demonstrated.[30-32] In this series, surfactant was applied to only 28% of cases. Worldwide, its use is reported in >80% of patients with weight <1 500 g.[33] Mortality among those who received at least one dose of surfactant was lower than among those who received no dose (23.6 *vs.* 32.4%), but this difference did not reach statistical significance. There was also no significant difference between those who received surfactant before or after 3, 6 or 12 h. Mortality is even higher among those receiving surfactant after 12 h of life when compared with those who did not receive surfactant (34.8 *vs.* 32.4%), without statistical significance. One possible explanation stems from the fact that, as a referral hospital, transfer of patients is requested and, despite the established therapies provided at a second-level of care, patients show no obvious improvement, i.e., the most seriously ill. Interhospital transfer, not always under the best conditions, can destabilize preterm infants, increasing the potential risk of hypoxia, acidosis, pulmonary hypertension and infection, contributing to mortality. Upon arriving in poor condition, with high requirement for assisted ventilation and with radiological images compatible with severe disease, an attempt has been made to provide surfactant treatment that we have now statistically proven is not useful and also implies considerable economic cost. The same is true for late preterm or term infants with high requirements for surfactant use and replacement therapy is offered. We add to this factor the enthusiasm of resident physicians to apply exogenous surfactant for training in this essential therapy in their future professional activities.

In the particular case of our patients, it has been possible to reduce mortality to 54% of what we reported in the early 1990s before the era of the surfactant.[16] Data presented here show that this improvement was not secondary to its use. Our intention was not to detract from a proven therapy under well-controlled conditions but to note that in the evolution and in reduction of mortality from HMD, advances in assisted ventilation have also participated with the use of more modern equipment. Personnel are better trained on their use. There is better monitoring of vital signs of the newborn, mechanical ventilation and oxygenation status in real time through hemoglobin saturation, better techniques for early detection of ductus arteriosus, cerebral hemorrhage and infection, and treatment of concomitant diseases (broad-spectrum antibiotics, immunoglobulin, vasoactive amines, analgesics and relaxants). These factors have been identified previously and act in conjunction with the surfactant and antenatal steroid use with a net result of decreased mortality.[34,35]

One limitation of this study is its retrospective nature because it has only data recorded in the clinical file. It is unknown whether some data are intentionally sought. By including a long time period, there is a risk that treatment protocols were changed and that some pathologies or sequelae are searched for differently. It is probable that some variables unknown to us influenced the response to surfactant. This study was not designed to evaluate the effectiveness of late-applied surfactant. Only association data are shown. Data found here may be useful in

other neonatal intensive care units without maternity care. Those units who do have them can apply surfactant early and obtain a higher success rate when taking into consideration part of the casuistry regarding premature infants with varying degrees of severity. Under the most controlled general conditions, the premature infant should not be mobilized under assisted ventilation.

In conclusion, HMD still presents a high mortality in our environment, mainly due to lower weight and gestational age along with certain maternal antecedents such as diabetes and threatened abortion. The use of surfactant has not managed to decrease HMD in this referral hospital.

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