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Recommendations for respiratory support in the newborn (III). Surfactant and nitric oxide☆

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Abstract The recommendations included in this document will be part of a series of updated reviews of the literature on respiratory support in the newborn infant. These recommendations are structured into twelve modules, and in this work module 7 is presented. Each module is the result of a consensus process including all members of the Surfactant and Respiratory Group of the Spanish Society of Neonatology. They represent a summary of the published papers on each specific topic, and of the clinical experience of each one of the members of the group.

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Recomendaciones para la asistencia respiratoria en el recién nacido (III). Surfactante y óxido nítrico

Resumen Las recomendaciones incluidas en este documento forman parte de una revisión actualizada de la asistencia respiratoria en el recién nacido. Están estructuradas en 12 módulos y en este trabajo se presenta el módulo 7. El contenido de cada módulo es el resultado del consenso de los miembros del Grupo Respiratorio y Surfactante de la Sociedad Española de Neonatología. Representan una síntesis de los trabajos publicados y de la experiencia clínica de cada uno de los miembros del grupo.

Surfactant

General concepts and types of surfactants

Pulmonary surfactant is a surface-active substance produced by type II pneumocytes and essentially formed by a lipoprotein complex. Phosphatidylcholine accounts for 70% of its lipid component, while four different types of surfactant proteins have been described in the literature, the most important of which are SP-B and SP-D.[1] The main function of surfactant is to reduce surface tension at the alveolar air–liquid interface, preventing the lungs from collapsing on expiration.

Starting at 22 weeks of gestation, during the canalicular period of foetal lung development, lamellar bodies loaded with surfactant can be found inside type II pneumocytes, but it is not until the end of this period that pulmonary development and the surfactant system are fully effective in guaranteeing an adequate gas exchange.

For this reason, children born before 34 weeks (sometimes up to 36) of gestation may have a deficiency of pulmonary surfactant, which is the cause of respiratory distress syndrome (RSD). This deficiency leads to alveolar collapse, producing respiratory distress, hypoxaemia and hypercapnia.

Surfactant therapy has revolutionised the care of these patients since its introduction in 1980. Combined with the use of corticosteroids for accelerating the antenatal maturation of the lungs and advances in respiratory support, it has contributed to an increase in the survival of preterm newborns. At present, surfactant administration is considered a safe and effective treatment, both as prophylaxis and rescue therapy, in newborns at high risk of developing RSD.

Many aspects of its use have been investigated in multiple multicentre controlled studies that have been subsequently analysed in systematic reviews.[2,3]

In recent years, different commercial preparations have been developed that vary in composition and clinical outcomes.[4] The most widely used are:

- *Synthetic surfactants:* they were the first type to be marketed. Colfosceril (Exosurf®), consisting solely of dipalmitoylphosphatidylcholine, is no longer available. Later on, lucinactant (Surfaxin®), whose composition includes a peptide that mimics the action of SP-B, was introduced in the market.
- *Natural surfactants:* they are basically classified into those derived from bovine (beractant, Survanta®) or porcine (poractant, Curosurf®) ground lung extracts and those derived from bovine bronchoalveolar lavage (calfactant, Infasurf®).

Treatment with natural surfactants has certain advantages over first-generation synthetic surfactants. Natural surfactants have shown a faster onset of action and a greater reduction in the number of fatalities and pneumothorax cases when compared with the first generation of synthetic surfactants.[5]

Lucinactant has been compared with natural surfactants. However, these studies were criticised due to early trial closures and inadequate sample sizes.[6–8]

Therefore, natural surfactants are currently the first-line treatment for RDS in preterm newborns (PTNBRDS), and no other type of surfactant is available in Europe. Thus, the decision we may face as neonatologists is which natural surfactant to use.

All the natural surfactant preparations differ slightly in their phospholipid and protein concentrations, as well as in the recommended dose for each patient measured in units of volume or milligrams per kilogram of body weight. Many randomised controlled trials have been conducted to try to find differences in clinical outcomes between the various preparations.[9,10] Some of these studies found faster improvements in oxygenation, reduced need for retreatment and lower mortality when patients were treated with poractant alfa compared to other natural surfactants such as beractant. The pharmacological and clinical data of these studies indicate that a dose of 200 mg/kg results in a higher half life and better outcomes in the acute patient, and this is the recommended dose.[11] However, the relatively small number of newborns that has been studied may not suffice to establish a generalised recommendation.

The American Academy of Pediatrics has concluded that there is no clear evidence that significant differences exist in the clinical outcomes of patients between the different available natural surfactant preparations.[2]

Indications

- *PTNBRDS:* is the main therapeutic indication for surfactant, which has been the standard treatment for more than two decades. Its use in this pathology is unquestionable, as it has been proven to reduce the risk of pneumothorax and interstitial lung disease, the need for mechanical ventilation, and neonatal mortality.[3,12–15]
- Exogenous surfactant has been used to treat other respiratory diseases that lead to the transient inactivation, insufficiency or dysfunction of pulmonary surfactant. There are few controlled studies on this subject to support generalised recommendations for surfactant indication and therapeutic strategies in these patients.
- *Meconium aspiration syndrome (MAS):* improved oxygenation and a reduced need for ECMO upon administration of 4 doses of surfactant at 6 h intervals has been reported.[16] Thus, the use of surfactant could be recommended in patients with more severe presentations of MAS and oxygenation indices greater than 15, and should start as soon as possible (ideally within six hours of birth).[17] Another possibility is bronchoalveolar lavage with surfactant, with demonstrated advantages over lavage with saline or placebo, although the optimal suction method and amount of surfactant have yet to be defined clearly.[18]
- *Pulmonary haemorrhage:* there are no randomised controlled clinical trials for this indication. An observational study found promising results, with a reduced need for respiratory support without additional complications.[19]
- *Pneumonia and sepsis:* data from experimental models and studies on newborns suggest that alterations in alveolar surface tension develop in the context of inflammation due to infection,[20] especially by *Pseudomonas*, syncytial respiratory virus and group B streptococcus. Lotze et al. conducted a clinical trial on full-term newborns with respiratory failure and found that in the subgroup of patients diagnosed with sepsis or pneumonia, surfactant therapy significantly improved oxygenation and reduced the need for ECMO.[21]
- *Other indications:* in recent years, surfactant therapy has also been used for respiratory distress of other aetiologies, such as diaphragmatic hernia and pulmonary hypertension.[4]

Administration and dosage

Surfactant must be delivered directly to the inside of the lung. Its administration can be performed by invasive and noninvasive means.

- *Invasive administration:* requires the placement of an endotracheal tube for surfactant instillation. Current recommendations call for the early use of CPAP from birth and administration of surfactant as required, followed by extubation at the earliest opportunity, the foundation of the INSURE method: intubate-surfactant-rapidly extubate to CPAP.[22] This approach has been shown to reduce the need for mechanical ventilation, but the debate continues, as the positive effects of prophylactic surfactant administration could be compromised by the short period of CPAP required by the INSURE method.
- *Noninvasive administration:* consists in the administration of surfactant without intubation while the patient breathes spontaneously.
- *Nebuliser administration:* this alternative requires further research and discussion, and technical problems in nebuliser devices need to be resolved.[23]
- *Administration without intubation:* consists in the administration of surfactant by means of a thin endotracheal tube or rigid catheter in spontaneously breathing patients while on noninvasive ventilatory support.[24] It requires laryngoscopy for tube placement and may cause damage, especially in active preterm newborns.
- *Pharyngeal administration:* in recent years, alternative conduits have been investigated, such as oropharyngeal delivery or administration by means of a laryngeal mask airway.[25]

Surfactant dosing depends on the commercial preparation due to differences in the amount of lipoproteins (Table 1). The European consensus guidelines for the management of neonatal RDS propose administration of poractant alfa in doses of 200 mg/kg, associated to better outcomes compared to 100 mg/kg doses of the same product or of beractant.[26]

The systematic review by Soll and Eren published in 2009 noted a reduction in the need for ventilatory support and in the incidence of pneumothorax, and a decreasing trend in mortality when multiple doses were used for the treatment of refractory respiratory insufficiency.[27] In the published studies, the administration regimen consisted of up to three doses, delivered at 12-h intervals while the patient continued to need oxygen therapy. However, it is not clear what the best retreatment schedule is. Natural surfactant manufacturers recommend different intervals, and different guidelines recommend different strategies. The European guidelines are not very specific and simply recommend a flexible course of treatment based on the need for mechanical ventilation and oxygen therapy.[26]

Some factors that may influence the retreatment schedule are the dose that was initially administered (200 mg/kg) and the presence of complicated RDS (infection, haemodynamic instability, perinatal morbidity).

All surfactants must be stored refrigerated at 2–8 °C and must be brought to room temperature before administration.

Methods of administration

Since the distribution of surfactant in the lungs depends mostly on gravity, it is recommended that the patient be kept in the horizontal supine position, with the head centred in the midline, and that surfactant be delivered by slow bolus infusion (over approximately 1 min).[28]

While different devices can be used in intubated patients, the use of double-lumen endotracheal tubes has been proven to be safe and efficacious, reducing the incidence of hypoxia and bradycardia episodes associated to surfactant administration.[29]

Prophylaxis versus rescue

Several clinical trials have tried to establish the optimal timing of surfactant administration during the course of

Table 1 Dosage of the different surfactant types.

Type	Surfactant	Recommended dose	Volume
Natural	Beractant (Survanta®)	100 mg/kg	4 mL/kg
	Calfactant (Infasurf®)	105 mg/kg	3 mL/kg
	Poractant (Curosurf®)	200 mg/kg	2.5 mL/kg
Synthetic	Lucinactant (Surfaxin®)	175 mg/kg	5.8 mL/kg

RDS. One meta-analysis of all these studies published by the Cochrane Review in 2001 reported that early administration of surfactant therapy either as prophylaxis (<30 min of life) or as early rescue treatment (<2 h of life in symptomatic patients) has been proven to decrease the risk of pneumothorax, death, and the combined outcome of death and bronchopulmonary dysplasia. The most significant results were found in the cohort of preterm infants less than 30 weeks of gestation that required invasive ventilatory support at birth.[30]

However, nowadays, with the increased prenatal administration of corticosteroids and the widespread use of CPAP in the delivery room, many preterm newborns can be treated without resorting to endotracheal intubation unless there is clinical evidence of RDS. There are probably no noticeable differences in clinical outcomes between prophylactic administration and very early rescue surfactant in the first 30 min of life, so intubation may be delayed until it is clearly needed. Based on the recently published literature, we can state that initial stabilisation with CPAP and administration of rescue surfactant if needed is as safe and efficacious as intubation, mechanical ventilation and surfactant administration immediately after birth in this group of patients as it concerns their clinical outcomes, and thus we join the recommendations established in Scandinavian countries.[31,32]

The decision of which approach to use in early respiratory management may be based on the identification of the risk population labelled extremely preterm newborns (without a specific overall definition of the cut-off gestational age) that have not been treated with antenatal corticosteroids.

Adverse effects

- *Airway obstruction:* occurs more frequently with higher-volume preparations, and can cause desaturation and/or bradycardia. Sometimes, part of the surfactant can be seen flowing back up the endotracheal tube.
- *Changes in cerebral blood flow:* the administration of surfactant in the context of respiratory distress produces an increase in the mean blood flow velocity in the middle cerebral artery that is sustained for up to 45 min following administration. Slow instillation of smaller volumes has been suggested as a possible strategy to minimise these haemodynamic changes.[9]

Recommendations

1. The administration of surfactant is safe and efficacious for the first-line treatment of RDS in preterm newborns (A).
2. It can be efficacious for the treatment of other acute respiratory pathologies (B).
3. Early rescue treatment is the most adequate therapeutic approach (A).
4. Double-lumen endotracheal tubes and noninvasive techniques are safe and effective means of administration (B).
5. The most appropriate regimen consists of an initial dose of 100–200 mg/kg (depending on the type of surfactant), with a maximum of three doses depending on the clinical response of the patient (A).

Inhaled nitric oxide

Rationale

Nitric oxide (NO) is a small gaseous molecule that is mainly produced by the alveolar and vascular endothelium from the amino acid L-arginine by the action of NO synthase. At the cellular level, it stimulates guanylate cyclase to increase intracellular cGMP, which has a powerful vasodilatory effect on smooth muscle tissue, promoting tissue perfusion wherever it is released.

Synthetic NO is manufactured for commercialization in gaseous form, and can be administered by inhalation (iNO) so that it diffuses quickly to smooth muscle tissues after reaching the alveoli, producing selective vasodilation of the pulmonary region and improving the ventilation/perfusion ratio wherever it is absorbed.

Its half-life ranges between 3 and 4 s, as it is rapidly inactivated in the bloodstream, giving rise to methaemoglobin (MetHb). For this reason, its effects do not extend beyond the area where it is absorbed.[33]

Therapeutic indications

The main therapeutic indication of iNO is pulmonary hypertension (PHT), be it primary or secondary to pulmonary pathologies (neonatal RDS, MAS, congenital diaphragmatic hernia, pneumonia) or associated with congenital heart diseases (both pre and post surgery).

Clinical trials conducted in late preterm (>34 weeks) or full-term newborns have observed that iNO improves oxygenation indices and reduces the need for ECMO and the incidence of bronchopulmonary dysplasia. However, it does not influence mortality, and the worst outcomes are found in newborns with diaphragmatic hernia.[34,35]

The results of published studies on the use of iNO in preterm newborns suggest that it can improve oxygenation but that it does not improve survival rates.[36]

On the other hand, the early use of low-dose iNO in preterm newborns does not improve the rate of survival without development of bronchopulmonary dysplasia

or brain damage, so it is not a satisfactory preventive strategy.[37]

Thus, treatment with iNO will be considered in patients with severe hypoxaemic respiratory failure and evidence of PHT (difference between pre- and postductal SpO_2 >5%, echocardiographic evidence) when they have an oxygenation index (OI) above 25 in two successive measurements at least 30 min apart ($IO = MAP \times FiO_2 \times 100/postductal\ PaO_2$). Some authors indicate that early initiation of treatment with iNO with OIs between 10 and 20 offers clinical benefits, reducing the amount of oxygen therapy and the need for ECMO.[38]

We cannot recommend the routine use of iNO for the treatment of respiratory failure in preterm newborns, and it will only be considered in cases of severe hypoxaemia as a rescue therapy, following optimisation of lung recruitment, and delivered in low doses (<10 ppm).

Practical management

1. Since iNO diffuses through the alveolar endothelium, it requires effective lung recruitment prior to its initiation. High-frequency ventilation can be used to achieve this when needed.
2. Previous optimisation of all factors that promote pulmonary vasoconstriction: optimisation of oxygenation, maintenance of a pH $\geq$7.40 with normocapnia (pCO_2, 45–40 mmHg), sedoanalgesia, normothermia, haemodynamic management, electrolyte normalisation (especially glucose and calcium) and correction of anaemia.
3. According to the Food and Drug Administration, iNO must be delivered using an appropriate system with a gas injector module capable of maintaining the concentration of iNO constant during the inspiratory flow. Furthermore, the time that iNO mixes with oxygen should be minimised to avoid the formation of potentially toxic gases, and the device should include a monitoring system, with alarms, for administered NO and O_2 and generated NO_2.[36]
4. Initiate iNO with 10–20 ppm (5 ppm in preterm newborns). Patients usually respond quickly, within the first 60 min (OI < 10, F_iO_2 < 70). A patient is considered to show a poor response if the postductal PaO_2 does not increase by 20% within 60–90 min, in which case higher doses may be tried of up to 40 ppm (10 ppm in preterm newborns), although improvement will rarely follow. Up to 40% of patients do not respond to iNO.
5. MetHb monitoring every 24 h.
6. In patients that do not respond, iNO will be weaned in a progressive and slow manner (halving the dose every 10–15 min to its discontinuation). In responsive patients, the dose of supplemental oxygen will be tapered down to 0.6 first, and then the dose of iNO will be reduced slowly until reaching the minimum effective dose. If oxygenation worsens as the dose is reduced (requirement increase >15% of previous requirement), the dose will be increased back to the previous amount and will be maintained for several hours before attempting weaning again.

Side effects

- *Methaemoglobinaemia*: results from the reaction of NO with haemoglobin, so that the latter cannot transport oxygen. It is recommended that the levels of methaemoglobin (MetHb) are monitored in all patients requiring treatment with iNO; the dose of iNO must be reduced when MetHb ranges between 2.5% and 5% (if the condition of the patient allows it) and iNO suspended when the level exceeds 5%. Preterm newborns are at higher risk of MetHb toxicity because they have lower levels of MetHb reductase.
- *Increased nitrogen dioxide* (NO_2) *concentration*: this results from the reaction of NO with high oxygen concentrations in the circuit and airway. Levels above 3 ppm can cause pulmonary damage, oedema and oxidative stress resulting from the production of peroxynitrite. However, this is an infrequent occurrence at the recommended doses.
- *Inhibition of platelet aggregation:* it can increase the risk of haemorrhage.

Conflicts of interest

The authors have no conflicts of interest to declare.

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