REVIEW ARTICLE

FACTORS AFFECTING RESPONSES OF INFANTS WITH RESPIRATORY DISTRESS SYNDROME TO EXOGENOUS SURFACTANT THERAPY

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ABSTRACT

Approximately 20% to 30% of infants with respiratory distress syndrome (RDS) do not respond to surfactant replacement therapy. Unfortunately there is no uniform definition of 'response' or 'non-response' to surfactant therapy. Response was based on improvement in a/A PO_2 and/or mean airway pressure (MAP) by some and on improvement in FIO_2 and/or MAP by others. Even the point of time at which evaluation of response was done is different in various reports. There is an urgent need to adopt an uniform definition.

Most premature babies are surfactant deficient which is the aetiological factor of RDS. Generally good antenatal care and perinatal management are essential in avoidance of premature birth. Babies with lung hypoplasia and who are extremely premature (less than 24 weeks of gestation) do not respond well to exogenous surfactant replacement because of structural immaturity.

Prompt management of asphyxiated birth and shock are necessary as there may be negative response to surfactant replacement.

Foetal exposure to glucocorticoids improves responsiveness to postnatal administration of surfactant. Antenatal steroid therapy has become an important part of management of RDS with surfactant replacement.

The premature lungs with high alveolar permeability tend to develop pulmonary oedema. With the presence of plasma-derived surfactant inhibitors, the response to exogenous surfactant may be affected. These inhibitors may also be released following ventilator barotrauma.

The standard of neonatal intensive care such as ventilatory techniques has an important bearing on the outcome of the RDS babies. Overloading of the pulmonary circulation through a patent ductus arteriosus (PDA) or from fluid overloading can be associated with poor response to surfactant therapy. Other factors including abnormal haematocrit, air leak can also be responsible for poor results.

One has to look into factors in relation to surfactant administration eg dosage, quality, timing, methods etc.

Exogenous surfactants are not a panacea for all problems of prematurity. It is imperative that prematurity should be prevented.

Keywords: *Pulmonary surfactant, exogenous; factors associated with non-response; respiratory distress syndrome.*

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INTRODUCTION

It has now been proven by many research trials that exogenous surfactant replacement therapy for the treatment of premature babies with RDS has been efficacious and impressive. This form of therapy results in reduction of severity of RDS, overall mortality as well as complications such as pulmonary air leaks etc. However, surfactant therapy does not solve all the problems of babies with respiratory distress. Approximately 20% to 30% of infants do not 'respond' to surfactant administration[1,2]. The reasons for failure to respond to exogenous surfactant treatment are not clear and many postulations have been propounded.

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Definition of 'Response' or 'Non-response'

When interpreting the findings to see the therapeutic response of surfactant replacement therapy, one is puzzled by the many different definitions of 'response' and 'non-response' adopted by various investigators. There were more than 10 different definitions in the medical literature. Many parameters were used including a/A PO_2 ratio, MAP (mean airway pressure), FIO_2 (fractional inspiratory oxygen concentration), VI (ventilatory index), VEI (ventilatory efficiency index), IMV rate (intermittent mandatory ventilation), PIP (peak inspiratory pressure) and radiology etc. Some investigators used only one parameter[3-5], others used a combination of 2 to 5 parameters[6-13] (Table I). Even the point of time at which evaluation was done was different, at 6, 12, 24, 36, 72 or 120 hours etc. Which end points should be used to judge the efficacy of surfactant? There is an urgent need to adopt an universal definition to evaluate the response of surfactant replacement therapy, at least for comparing the early responses.

It is important to note that a good early/acute response does not always associate with good outcome. Is transient improvement in respiratory function sufficient for assessment of drug efficacy? Transient improvement without salutary effect on survival and reduction in the frequency or severity of BPD must continue to be viewed with skepticism. Adverse neurodevelopmental outcome should also be reduced from

surfactant therapy[14]. It is also noted that those who did not appear to have an early response to treatment may subsequently have improved survival.

Table I – Parameters used in Defining Response to Surfactant Therapy or Severity of RDS

Ref.	Parameters / Investigations	a/A pO2	MAP	FIO2	VI	IMV rate	VEI	PIP	Radiology	Evaluated at (hours old)
3	Charon et al	+								12,24,48
4	Collaborative European Multi-centre study	+								24
5	Segerer et al			+						6,8-60
6	Fujiwara et al	+	+							24,120
7	Hallman et al		+	+	+					1,6,12,24,48 72,96,120,144
8	Enhorning et al	+		+	+					72
9	Soll et al	+	+	+					+	24,72
10	Dunn et al	+		+	+					6,12,18,24,36 48,72,96,120
11	Shapiro et al		+	+						24,48,72
12	Kwong et al		+	+		+	+		+	48
13	Shennan et al			+				+		24

RDS (Respiratory Distress Syndrome)
MAP (Mean Airway Pressure)
FIO2 (Fractional Inspiratory Oxygen Concentration)
VI (Ventilatory Index)
IMV (Intermittent Mandatory Ventilation)
VEI (Ventilatory Efficiency Index)
PIP (Peak Inspiratory Pressure)

FACTORS ASSOCIATED WITH NON-RESPONSE TO SURFACTANT THERAPY

Some perinatal factors

The Immature Lungs

The more premature the baby, the more immature is the lung structure. The structurally immature lungs limit pulmonary function especially in babies who are less than 24 weeks in gestation[15]. Other than surfactant deficiency, there are also other lung-immaturity problems. The immature lungs have high alveolar permeability and plasma-derived surfactant inhibitors can accumulate in the airways soon after birth and following mechanical ventilation. The severity of respiratory failure, aggravated by oedema fluid, depends on the amount of surfactant inhibitors and the pool size of surfactant. It is therefore imperative to provide good antenatal and perinatal care in order to avoid or delay premature births.

Lung Hypoplasia

In lung hypoplasia, inadequate gas exchange and poor lung function are expected and exogenous surfactant has little or no effects on these patients.

Persistent Pulmonary Hypertension of the Neonate (PPHN).

There was evidence of surfactant deficiency in persistent foetal circulation[16]. Whether early surfactant administration is beneficial for preventing PPHN is uncertain. Further studies are required.

The Infected Lungs

A lot of interest has been generated in the expanded role of surfactant replacement therapy. Randomised controlled studies to examine the efficacy of surfactants in infants with meconium pneumonia are being done. At the present moment, exogenous surfactant should be confined to the treatment of RDS. Two common infected lung disorders in the neonate are seen: the meconium aspiration pneumonia and the bacterial pneumonia.

a) Meconium Aspiration Pneumonia

It was studied that meconium diluted to 6500 times was able to inhibit surfactant function[17]. Theoretically, exogenous surfactant in very high concentrations could reverse the inhibitory effects of meconium. Some centres are conducting clinical trials on these.

b) Bacterial Pneumonia

Bacteria secrete a variety of phospholipases which can inhibit the function of surfactant[18]. For the same reasons, it is postulated that high concentration of exogenous surfactant might have a role in these disorders.

Birth Weight and Gender

The birth weight is a strong determinant for gestational age. The more premature the baby, the lighter the weight. It is so much more easily measurable than gestational age and it is often used as a criterion for study of premature babies. In the absence of other reliable parameters, birth weight can be taken for consideration of gestational age.

There may be some differences in the severity of RDS in baby girls and boys. The females tend to be less severe and the response to surfactant may be better. However, it is not so in our experience[2].

There may be some differences in the severity of RDS as well as response to surfactant replacement therapy in babies from different racial groups. Investigators should look into these.

Birth Asphyxia

Asphyxia is an important determinant of decompensation from left to right shunt through a PDA[19]. It is also the important cause of acute left ventricular failure. Fujiwara[6] reported a 6% incidence of poor response in his patients, all of whom had severe perinatal asphyxia. The severity of the lung oedema can also be contributed by asphyxia.

Pulmonary Oedema

Pulmonary oedema has been associated with poor response to surfactant therapy. The cause of pulmonary oedema can be due to congestive cardiac failure, the presence of a significant PDA etc. The exogenous surfactant is therefore inactivated, inhibited or diluted.

Shock

Babies who are in a state of shock responded poorly to surfactant therapy. It is dangerous to administer surfactant as it had been shown in animal experiments that there was an acute dramatic fall in blood pressure and cardiac output, as well as an increase in pulmonary vascular resistance following surfactant therapy. Such phenomenon is known as 'negative responsiveness'[20].

It follows that baby with blood volume depletion can also react with 'negative responsiveness'.

Antenatal Maternal Steroids or Other Drug Therapy

Foetal exposure to steroids improves responsiveness to postnatal administration of surfactant. The lungs are altered such that less surfactant is required to prevent RDS. It was reported that only about 10% or 15% of babies in the United States received antenatal steroids. Obstetricians should be convinced that steroid therapy is worthwhile. In Singapore, 33% of mothers of the premature babies who were diagnosed to have RDS and required surfactant therapy had antenatal steroids[2]. Animal studies have shown that steroid treatment has little effect on alveolar surfactant pool size[21] but enables the foetal lungs to be more responsive to surfactant. A study using bovine surfactant revealed those with maternal steroids had decreased

incidence and severity of complications of prematurity such as severe intraventricular haemorrhage (IVH), bronchopulmonary dysplasia (BPD) and air leak[22].

Other antenatal drugs may also be helpful to reduce the severity of RDS. Thyrotropin releasing hormone (TRH) given together with steroids, have been shown to produce better response to surfactant treatment[23]. Epidermal growth factor (EFG)[24,25] which accelerates maturation of both gas exchange and conducting airways of the foetal lungs in foetal lambs and in rhesus monkeys, may find a place in clinical use.

Maldistribution of surfactant was suspected to be a factor for poor response to treatment in some infants. However, it was not found to be so in a study using a radionucelide label and lung scanning[3].

II. FACTORS RELATED TO NEONATAL CARE PRACTICES

In clinical trials of exogenous surfactant replacement, the treatment practices of various neonatal intensive care units (NICUs) were not 'controlled'. However, certain styles of treatment may affect the response of surfactant therapy.

The Styles of Assisted Ventilation

Differences in surfactant responsiveness may be due to different ventilatory treatment practices. Different NICUs have different styles of assisted ventilation. The pattern of ventilation might also result in improved intrapulmonary distribution of the surfactant, followed by improved distribution of ventilation. Some NICUs used inspiratory time as long as 1 second[6] whilst other NICUs ventilate babies at shorter inspiratory time[26]. Even the weaning policies from assisted ventilation after improvement with surfactant replacement are also different. In some NICUs, the primary aim was to reduce ventilatory pressure first in order to avoid barotrauma, air leaks, pneumothorax or over-distension of the lungs after lung compliance has been increased by surfactant. However, in other NICUs, the primary aim was to lower the ambient oxygen concentration first.

The effect of the standard of ventilatory care on the response to surfactant replacement therapy cannot be ignored. Complications may occur at the narrowed window of time when the babies respond dramatically to exogenous surfactant. Surfactant administration must be done by trained staff so that ventilatory adjustment can be done immediately. Ventilatory settings should be maintained optimally. Too rapid reduction of ambient oxygen concentration or too early lowering of peak inspiratory pressure are both harmful to the improving baby as desaturation can occur.

Some centres claimed a better outcome of babies treated with surfactant if the babies were also managed with high frequency ventilation, either with high frequency jet ventilation (HFJV)[27] or by high frequency oscillatory ventilation (HFOV)[28].

Fluid management

Excessive fluid infusion may lead to impaired respiratory function and poor response to exogenous surfactant treatment. Hallman found in his prospective study that liquid intake (intravenous fluids, drugs, and enteral nutrition) during the first 48 hours correlated with the degree of respiratory failure at the age of two days[29].

Presence of Patent Ductus Arteriosus (PDA)

PDA is characterised by increased pulmonary permeability which enhances the significance of the increased left-to-right blood flow through a PDA. A large left-to-right shunting across the PDA can adversely affect the response to surfactant therapy because pulmonary oedema crosses into the alveoli can inhibit surfactant function. It appeared that the incidence of BPD, IVH and air leak was lower in those babies who had no PDA[3]. The presence of PDA is one of the most important predictors of a non-response to surfactant replacement.

The risk of developing PDA with congestive cardiac failure in premature infant can be aggravated by increased fluid load[30,31].

The Damaged Lungs

Following barotrauma from mechanical ventilation, there is leakage of plasma-derived proteins into the airways and alveoli. Inactivation of exogenous surfactant can occur. Some clinicians therefore advocate early administration of surfactant before bronchiolar epithelial disruption occurs. Some recommended the use of high frequency ventilation to avoid pulmonary trauma. It has also been found that poor response to surfactant replacement therapy was associated with higher incidence of air leaks[3].

"Learning Curve" in Surfactant Management

Experience in the use of exogenous surfactant builds up after a period of time. The NICU staff who manage the very sick babies will acquire better skill and are able to respond promptly during the phase of rapidly changing lung function and circulatory readjustment that follow surfactant replacement. These are the important factors in bringing about better response in surfactant replacement therapy.

III. FACTORS RELATED TO THE USE OF EXOGENOUS SURFACTANT

Dosage of Exogenous Surfactant and the Number of Doses Administered.

The amount of phospholipids are different in the biological and synthetic surfactants. It is 100 mg/kg and 67.5 mg/kg respectively. Berry and Konishi using different types of surfactant showed in separate studies more benefit by giving larger dose[32,33]. Many randomised trials have shown that multiple doses of surfactant are more beneficial than single-dose treatment[10,34-36]. The total number of doses to be given is currently not clear, though a recent report of an international multicentre trial on synthetic surfactant showed that the option to give the third and fourth doses of synthetic surfactant when signs of RDS persist or recur conveyed no clinical benefit over the standard regimen of 2 doses[37]. Similarly, the frequency of administration, to give 8- or 12-hourly, is also not certain.

The Types of Surfactant - Synthetic or Biological

There are many types of exogenous surfactant. The biological sources include the bovine (Survanta, Infasurf), porcine (Curo surf) or human prepared from amniotic fluid. Surfactants which contain no protein materials and are synthetically prepared include Exosurf Neonatal and ALEC (artificial lung expansion compound). Non-responders were seen in all these types of surfactant. (24% of non-responders in the group were treated by porcine surfactant[4], 6% to 22%, by bovine surfactant[3,6]; and 18% to 24%, by synthetic surfactants[2,13]. There appears to be a difference in the restoration of lung function when comparing biological with synthetic surfactants (biological - more immediate effects on lung function, oxygenation and ventilation)[38]. In terms of clinical outcome, the difference may not be significant.

Prophylactic, Early or Rescue Surfactant Treatment

Currently it is still not clear which method is more superior and has better responsiveness as study results are conflicting [39-42]. A global study using synthetic surfactant was released recently.

Infants allocated to early administration (within 2 hours of life) were less likely to be dead or oxygen-dependent at 28 days of age or on the 'expected date of delivery' or to die at any time, or to sustain a pneumothorax[37].

Methods of Administration

The methods of surfactant administration may affect the outcome of management. For instance haemodynamic changes which occurred after bolus surfactant administration may disturb the cerebral blood flow, thus increasing the risk of intraventricular haemorrhage[43]. Nebulisation of exogenous surfactant may be hampered with low bioavailability. It is not clear whether positioning of the baby during surfactant instillation can affect the results. Even administration of other drugs such as indomethacin can have adverse effects on haemodynamics. Bolus administration of indomethacin tends to be associated with reduction in cerebral arterial blood flow[44]. When given over 30 to 60 minutes, changes in cerebral blood flow velocity may be reduced.

IV. WHO SHOULD GIVE SURFACTANTS AND WHERE?

Surfactant replacement therapy improves survival rate and reduces severity of RDS. Nevertheless one has to follow up the patients to see the improvement of overall outcome from treatment. The Committee on Fetus and Newborn of the American Academy of Pediatrics expressed concerns regarding potential misuse of this form of therapy when it becomes widely available. Caring for the RDS infants in nurseries that do not have the full range of capabilities required may affect the overall outcome adversely. In outlining the recommendations for surfactant replacement therapy in 1991, the committee recommended that surfactant replacement therapy should be conducted by qualified physicians with experience in respiratory management of low birth weight infants and in mechanical ventilation[45]. It was also recommended that surfactant be given in institutions which fulfilled the requirements listed, except when emergency situation arises.

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