
History of Surfactant from 1980

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Key Words

Surfactant · Preterm infant · Respiratory distress syndrome · Continuous positive airway pressure · Clinical trials · History

Abstract

The first successful trial of surfactant treatment for respiratory distress syndrome (RDS) was reported in 1980. Since then there have been numerous randomised trials demonstrating first, the efficacy of surfactant treatment in reducing pulmonary air leaks and increasing survival and second, assessing various other aspects of therapy. These studies show that multiple doses may be needed if surfactant is used to treat established RDS but early or prophylactic treatment is superior for infants with gestational ages less than 30 weeks. Natural surfactants (containing proteins) are more effective than synthetic products (protein free), the latter now being infrequently used. Natural surfactants vary and should not be considered to be equivalent in their effects. A porcine surfactant (poractant alfa) acts more rapidly than a bovine preparation (beractant) in infants with moderate to severe RDS. A meta-analysis of 5 comparative studies suggests that a dose of 200 mg/kg of poractant alfa is associated with lower mortality compared with 100 mg/kg of beractant. Chronic lung disease remains a problem but it is hoped that early treatment with surfactant combined with extubation to continuous positive airway pressure will reduce this complication of prematurity. The newer synthetic surfactants, containing analogues of surfactant protein B or C, have undergone some trials for treatment

of RDS but comparative studies which have just been published do not show that they are superior to existing natural surfactants. However, as they are more resistant to inactivation they may have a role in treatment of adult or acute RDS. The last 25 years have seen a large increase in basic science research on surfactants with determination of the structure and function of the four surfactant proteins probably being the most important advances. Future studies will focus on widening the indications for surfactant treatment, developing non-invasive means of administration and assessing the role of the newer synthetic surfactants.

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Introduction

My remit is to summarise the history of surfactant from 1980 following on from Obladen's [1] excellent description of the history prior to this. As he ended with the classic paper of Fujiwara et al. [2] in 1980, I will continue from there. Since my interests have focused on studies using a porcine lung-derived surfactant and the preparation of systematic reviews for the Neonatal Review Group of the Cochrane Collaboration, my history will be based on these two themes. As there have been many trials of surfactant replacement since Fujiwara et al. first published their results, it is necessary to summarise outcomes using the many systematic reviews prepared by Soll and his colleagues [3–11] and published in the Cochrane Library. I will discuss the clinical trials beginning with the pilot studies in the early 1980s, continue with the ran-

domised trials designed to answer various questions about surfactant treatment, and end by mentioning the landmark basic science studies underpinning surfactant therapy since 1980.

Pilot Trials

The pilot trials of the early 1980s used either synthetic (protein free) or natural (derived from animal lungs or human amniotic fluid) surfactants (table 1). Only one pilot trial of a synthetic surfactant was reported and this involved artificial lung-expanding compound [12], although the new synthetic surfactant lucinactant (Surfaxin) has also been studied quite recently in an uncontrolled series of infants with respiratory distress syndrome (RDS) [13]. A number of natural surfactants were used in the pilot trials and these included calf lung surfactant extract [14], human surfactant (derived from amniotic fluid) [15], poractant alfa (Curosurf) [16], and SF-RF 11 (Alveofact) [17]. These pilot trials were uncontrolled and most were able to replicate the findings of Fujiwara et al. [2] in showing improvement in oxygenation. The scene was set for the first randomised controlled trials of surfactant.

Randomised Controlled Trials

Many of the early randomised controlled trials of surfactant replacement contained small numbers and were under-powered to detect worthwhile long-term outcomes [18–21]. These were all prophylactic studies and most used natural surfactants but individually they were not able to show significant reductions in neonatal mortality. Some time later 2 meta-analyses of prophylactic surfactant studies with natural [3] and synthetic [4] surfactants were able to demonstrate significant reductions in neonatal mortality [typical relative risk (TRR) 0.60; 95% confidence interval (CI) 0.44–0.83 and 0.70; 0.58–0.85, respectively].

Prior to this, however, in 1988 it had been shown that a natural surfactant derived from porcine lungs [22] was able to significantly reduce neonatal mortality from 51 to 31% ($p < 0.05$) in a single-dose rescue trial of severe RDS [23]. This, the first randomised clinical trial of Curosurf led to a series of further trials that investigated various aspects of surfactant treatment: single versus multiple doses [24], early versus late treatment [25], high- versus low-dosing regimens [26], prophylaxis versus rescue treatment [27–29], use of surfactant with nasal continuous

Table 1. Surfactants used in clinical trials

Old synthetic (protein-free)
Pumactant (ALEC)
Colfosceril palmitate (Exosurf)
Turfsurf (Belfast surfactant)
New synthetic (protein analogues)
Lucinactant (Surfaxin)
rSP-C surfactant (Venticute)
Natural 1 (minced lung extracts)
Surfactant TA (Surfacten)
Beractant (Survanta)
Poractant alfa (Curosurf)
Natural 2 (lung lavage extracts)
CLSE (bLES)
Calfactant (Infasurf)
SF-RF 11 (Alveofact)
Natural 3 (amniotic fluid extract)
Human surfactant

rSP-C = Recombinant surfactant protein C; ALEC = artificial lung-expanding compound; CLSE = calf lung surfactant extract.

positive airway pressure (CPAP) [30, 31], and finally comparative trials with other surfactant preparations [32–37]. The 3 prophylaxis versus rescue studies have been the subject of a meta-analysis [38] and the results of this are shown in table 2. Further analysis of the data from the prophylaxis versus rescue studies showed a significant reduction in severe intraventricular haemorrhage in the prophylactically treated infants, especially those who were outborn [39].

The results of these many randomised trials show that Curosurf improves survival in infants with severe RDS, is more efficacious if used with multiple (up to 3) doses rather than a single dose, is better used early or prophylactically in infants less than 31 weeks' gestation, may be beneficial when used with CPAP and seems to be superior to several other surfactant preparations, especially those of synthetic origin (table 2). These findings are very similar to those published in the various systematic reviews in the Cochrane Library [3, 6–10] and elsewhere [40, 41].

Natural surfactant preparations have been shown to be superior to synthetic ones in a number of trials summarised in systematic reviews [9, 41]. Use of natural surfactant reduces the risk of pneumothorax and improves survival compared to synthetic (protein-free) surfactants. Recently, there have been studies comparing the different

Table 2. Summary of results from randomised trials of Curosurf

Ref.	Year	Study	Findings
23	1988	First RCT	Improved oxygenation, reduced PIE and PTX, improved survival compared to controls
24	1992	Single vs. multiple doses	Improved oxygenation, reduced PTX, improved survival with multiple doses
25	1993	Early vs. late treatment	Improved survival and reduced severe IVH with early treatment
26	1993	High vs. low dose	Improved oxygenation up to 36 h with high dose, but no long-term benefits
38, 39	1997, 2002	Prophylaxis vs. rescue	For babies <31 weeks less severe RDS, less CLD, less severe IVH, and improved survival with prophylaxis
30, 31	1994, 1999	Surfactant and CPAP	Combination allows earlier extubation and may improve survival in infants <30 weeks
32–37	1995–2005	Comparative trials	Curosurf is superior to ALEC – improved survival Curosurf acts more rapidly than Survanta and may improve survival (see table 3)

RCT = Randomised controlled trial; PIE = pulmonary interstitial emphysema; PTX = pneumothorax; IVH = intraventricular haemorrhage; RDS = respiratory distress syndrome; CLD = chronic lung disease; ALEC = artificial lung-expanding compound.

natural surfactants [32, 35–37, 42, 43] and these have been summarised in a systematic review [44]. This review suggested that Curosurf reduces the need for re-dosing, is associated with fewer complications of administration, leads to better short-term oxygenation, and may reduce mortality compared with Survanta [44]. Only 3 randomised trials were included in this meta-analysis, and therefore the review was incomplete.

Systematic Review of Curosurf versus Survanta

This meta-analysis was performed using 5 studies [32, 35–37, 45] obtained after searching MEDLINE and using expert informants. A subgroup analysis based upon dose of surfactant (100 and 200 mg/kg) was pre-specified. For the purpose of this mini-review the outcome assessed was neonatal mortality and data analysis was performed using Revman (Cochrane Collaboration). Results are given as relative risks (RR) and numbers needed to treat (NNT) both with their 95% CI. As one study [36] compared 2 doses of Curosurf (100 and 200 mg/kg) with 1 dose of Survanta (100 mg/kg), it was considered as 2 separate studies with 1 comparison group. This meant that 6 studies were included in this meta-analysis (table 3). When all the studies are considered together, there is a significant reduction in neonatal mortality (RR 0.57, 95% CI 0.34–0.96) favouring Curosurf-treated infants. The NNT is 20

Table 3. Studies comparing Curosurf and Survanta: neonatal mortality

Ref.	First author	Year	Dose of Curosurf mg/kg	Curosurf n/N	Survanta* n/N
32	Speer	1995	200	1/33	5/40
45	Halihakoon	1999	100	5/17	3/10
35	Baroutis	2003	100	5/27	6/26
36	Ramanathan	2004	200	3/99	8/98
36	Ramanathan	2004	100	6/96	8/98
37	Malloy	2005	200	0/29	3/29
Total				20/301	33/301

* Survanta dose was 100 mg/kg; n = number of deaths at 28 days; N = number in the group.

Table 4. Relative risks and numbers needed to treat for neonatal mortality: Curosurf vs. Survanta

	n	RR	95% CI	NNT	95% CI
All studies	602	0.57	0.34–0.96	20	11–1000
Curosurf 100 mg/kg	274	0.82	0.44–1.55	–	–
Curosurf 200 mg/kg	328	0.29	0.10–0.79	14	8–50

n = Number; RR = relative risk; CI = confidence interval; NNT = number needed to treat.

but the 95% CI are wide, from 11 to 1,000 (table 4). When only studies using 100 mg/kg initial dose of Curosurf are considered, the reduction in mortality is not statistically significant (RR 0.82, 95% CI 0.44–1.58). This means that the most significant effect on mortality is seen when 200 mg/kg of Curosurf is compared with 100 mg/kg of Survanta (RR 0.29, 95% CI 0.10–0.79) with an NNT of only 14 and 95% CI from 8 to 50 (table 4). All these studies were treatment trials of infants with moderate to severe RDS and the evidence would suggest that for these infants the larger dose of Curosurf is more effective. For prophylaxis a lower dose of surfactant may be appropriate but so far there have been no published comparative trials to show this.

Studies with the new synthetic surfactants have been undertaken but so far there are no publications to suggest that they are better than existing natural surfactants [46]. As they are more likely to resist inactivation from components reaching the alveoli from the circulation, it is likely that the new synthetic surfactants may have a role to play in patients with ARDS [46, 47].

Surfactant for Meconium Aspiration

There have been at least 4 randomised trials of surfactant to treat severe meconium aspiration in term infants [48–51]. Two studies used bovine surfactant (Survanta), one with a dose of 150 mg/kg as a continuous infusion over 20 min and repeated 6-hourly for a maximum of 4 doses [48] and one with a dose of 100 mg/kg allowing up to 4 doses prior to extracorporeal membrane oxygenation and 4 additional doses if extracorporeal membrane oxygenation was required [49]. In a meta-analysis of these 2 studies Soll and Dargaville [11] concluded that surfactant administration reduced the severity of illness and the need for extracorporeal membrane oxygenation. A third study assessed the effects of lucinactant (Surfaxin) administered by lung lavage for infants with severe meconium aspiration [50]. There were no significant benefits from this procedure and 20% of infants had to have the lavages halted because of adverse effects such as hypoxaemia, bradycardia, and blood-stained aspirates [52]. Recently a study from China has assessed the effects of Curosurf in infants with severe meconium aspiration syndrome [51]. There was improved oxygenation but no significant reduction in mortality or morbidity. Surfactant treatment is still not an established treatment for meconium aspiration and further studies are warranted.

Basic Science Advances since 1980

The most important developments in basic research into the pulmonary surfactant system in the past 25 years have involved the surfactant proteins and elucidation of their structure and function [53]. This has been achieved by a collective effort from pathologists, physiologists, surface chemists, molecular biologists, and clinicians. Surfactant protein A (SP-A), which is the most abundant protein in pulmonary surfactant, is related to the collectins, a family of water-soluble proteins containing both collagenous regions and lectin domains [54]. SP-A has an important role in surfactant turnover, tubular myelin formation, and immunological regulation [55]. It also has a role in preventing surfactant inactivation and in host defence [56]. SP-D is a similar hydrophilic collagenous glycoprotein which is synthesised and secreted by type II pneumocytes and Clara cells [56] and with a major role in host defence. Transgenic mouse models of SP-A [57] and SP-D [58] deficiency have been developed in recent years. SP-A-deficient mice have normal lung function at birth despite a decreased production of tubular myelin. They are especially prone to die with infections such as those caused by group B streptococci and pseudomonas species. SP-D-deficient mice have large alveoli and chronic inflammatory changes in their lungs.

SP-B and -C are small, hydrophobic proteins necessary for surfactant function *in vivo*. SP-B-deficient mice develop a lethal form of RDS [59]. SP-B deficiency has also been recognised as a rare inherited cause of lethal respiratory distress in infancy [60] and more recently other genetic abnormalities leading to respiratory failure in infancy have been recognised and characterised [61]. There will be future developments in understanding the genetics of neonatal respiratory disorders including RDS and chronic lung disease which may lead to more rational therapies for both conditions.

Conclusions

The past 25 years of research and discovery in surfactant therapy have been both exciting and dramatic. On the clinical front numerous randomized trials have been performed to demonstrate that surfactant has been a major development in the treatment and prevention of RDS. Its role in the management of other conditions, such as meconium aspiration syndrome and congenital pneumonia, are less clear but there may be benefits from its use. Future trials should concentrate on determining other in-

dications for surfactant treatment, developing less invasive means of administration [62], evaluating its use with other interventions, such as inhaled nitric oxide or CPAP, and testing the new synthetic surfactants which contain analogues of SP-B and -C.

Basic science has allowed the structure and function of most surfactant components, both phospholipids and proteins, to be determined mainly during the last quarter of a century. Future developments will focus on producing

new surfactants that mimic all the various functions of natural surfactant and are resistant to inactivation, so widening the potential indications for surfactant treatment.

In conclusion, surfactant therapy has been one of the greatest advances in neonatology over the past 25 years and its introduction into clinical practice has increased survival of very low birth weight infants [63, 64] leading to a decreased use of resources [64] without any increase in long-term morbidity [65].

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