Review

Bench-to-bedside review: Paediatric viral lower respiratory tract disease necessitating mechanical ventilation – should we use exogenous surfactant?

Martin CJ Kneyber[1], Frans B Plötz[1] and Jan LL Kimpen[2]

[1]Department of Pediatric Intensive Care, VU University Medical Center, Amsterdam, The Netherlands
[2]Department of Pediatrics, Wilhelmina Children's Hospital, Utrecht, The Netherlands

Corresponding author: Martin CJ Kneyber, m.kneyber@vumc.nl

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Abstract

Treatment of infants with viral lower respiratory tract disease (LRTD) necessitating mechanical ventilation is mainly symptomatic. The therapeutic use of surfactant seems rational because significantly lower levels of surfactant phospholipids and proteins, and impaired capacity to reduce surface tension were observed among infants and young children with viral LRTD. This article reviews the role of pulmonary surfactant in the pathogenesis of paediatric viral LRTD. Three randomized trials demonstrated improved oxygenation and reduced duration of mechanical ventilation and paediatric intensive care unit stay in young children with viral LRTD after administration of exogenous surfactant. This suggest that exogenous surfactant is the first beneficial treatment for ventilated infants with viral LRTD. Additionally, *in vitro* and animal studies demonstrated that surfactant associated proteins SP-A and SP-D bind to respiratory viruses, play a role in eliminating these viruses and induce an inflammatory response. Although these immunomodulating effects are promising, the available data are inconclusive and the findings are unconfirmed in humans. In summary, exogenous surfactant in ventilated infants with viral LRTD could be a useful therapeutic approach. Its beneficial role in improving oxygenation has already been established in clinical trials, whereas the immunomodulating effects are promising but remain to be elucidated.

Introduction

Each winter paediatric intensivists are challenged with infants and young children with viral lower respiratory tract disease (LRTD) necessitating mechanical ventilation (MV). In the majority of cases the causative agent is respiratory syncytial virus (RSV), although other viruses such as the parainfluenza virus, human metapneumovirus, adenovirus and influenza virus have also been implicated [1-4]. The number of infants hospitalized with RSV LRTD in the USA annually is currently above 100,000 and still rising [5]. Respiratory failure necessitating MV occurs in 2–16% of previously healthy infants. This percentage may increase to 36% in prematurely born infants or infants with chronic lung disease [6,7]. The duration of MV may be as long as 10 days [8]. The efficacy of corticosteroids or ribavirin in reducing the duration of ventilation and of stay in the paediatric intensive care unit has not been demonstrated [9].

From a pathophysiological point of view, the use of exogenous surfactant seems rational. It was initially identified as a complex of lipids and proteins found at the air–liquid interface of the lungs, where its main function is to lower the surface tension [10-12]. A novel function of surfactant came from the emerging evidence that two surfactant proteins (SPs), namely SP-A and SP-D, are involved in the host immune response to various micro-organisms, including viruses [13]. This novel function gained further interest when it was found that these SPs are also expressed outside the lungs.

The purpose of this article is to review the role of pulmonary surfactant in the pathogenesis of paediatric viral LRTD necessitating MV, and the potential role of exogenous surfactant as a treatment modality. These functions of surfactant are discussed separately.

Composition of pulmonary surfactant

Pulmonary surfactant is a mixture of approximately 90% lipids and 10% proteins, synthesized within type II alveolar cells and secreted in the alveoli through exocytosis [14]. The best known function of surfactant is to lower surface tension at the air–liquid interface in alveoli and conducting airways, but it also enhances the transport of fluid from the alveolar space to the interstitium and improves mucociliary transport [10,14]. Reduction in surface tension is achieved by the lipid part of surfactant, which is composed of 90% phospholipids and

BAL = bronchoalveolar lavage; LRTD = lower respiratory tract disease; MV = mechanical ventilation; RSV = respiratory syncytial virus; SP = surfactant protein.

Table 1

Surfactant composition and function in mechanically ventilated children with viral (respiratory syncytial virus) lower respiratory tract disease

Reference	Study population (*n*; index/controls)	RSV+ patients (*n*)	Specimens	Study item	Index patients	Control patients
[21]	12/8	11/12	ET	SP-A	1.02 (0.35–4.67) μg/ml*	14.4 (5.6–58.7) μg/ml
				PC	350 (140–540) μg/ml*	1060 (690–4020) μg/ml
				MST	44 (42.5–45)*	34 (26–37)
[22]	30/35	27/30	ET	SP-A	2.4 ± 2.0 μg/ml*,[a]	12.8 ± 14.7 μg/ml
				SP-B	14.0 ± 19.3 μg/ml[a]	19.8 ± 29.8 μg/ml
				L/S ratio	11.2 ± 5.7*	41.8 ± 62.7
				PC	82.4 ± 62.1	120.5 ± 73.4
				Sphingomyelin	9.2 ± 7.9	8.1 ± 8.6
[23]	24/19	18/24	BAL	PG absent	8*	0
				Surfactant activity present	2*	12
[24]	18/16	18/18	BAL	SP-A	5.6 (0.6–151.9) μg/ml*	9.0 (0.5–139.6) μg/ml
				SP-B	12.0 (0.0 – 60.8) ng/ml*	118.1 (0.0–778.2) ng/ml
				SP-D	130.3 (0.0–148.6) ng/ml*	600.4 (0.0–1869.0) ng/ml

Values are expressed as mean (range) or mean ± standard deviation. [a]Expressed as quantity per total protein amount. BAL, bronchoalveolar lavage; ET, endotrachael aspirate; L/S, lecithin/sphyngomyelin; MST, mean surface tension; PC, phosphatidylcholine; PG, phosphatidylglycerol; RSV, respiratory syncytial virus; SP, surfactant protein. *$P < 0.05$.

10% phosphatidylglycerol [11]. Four SPs, designated SP-A, SP-B, SP-C and SP-D, play an important role in surfactant homeostasis and protection against inhibition by plasma proteins or serum [10,11,14,15].

Emerging data demonstrate that SP-A and SP-D also mediate a host defence function [16]. For SP-B and SP-C no data are available on the influence of these proteins on the host immune response. SP-A and SP-D have a calcium-dependent lectin domain (the so-called carbohydrate recognition domain), which is usually the binding site for micro-organisms. SP-A is a octadecamer molecule composed of six trimeric subunits, which is formed like a bouquet of tulips [17]. Its main function is opsonization and phagocytosis of micro-organisms by antigen-presenting cells such as alveolar macrophages. SP-D is composed of four trimeric subunits, and it is a very potent mediator in collectin-mediated viral aggregation with subsequent clearance of virus through uptake by phagocytes [17-19]. Both proteins are expressed in alveolar type II cells, although SP-A is not only expressed in Clara cells and cells in tracheobronchial glands but also outside the lungs [15,19,20].

Impairment of surface tension reduction in viral lower respiratory tract disease

Observational studies conducted in mechanically ventilated infants with viral LRTD have demonstrated lower concentrations of surfactant lipids in bronchoalveolar lavage (BAL) fluids or endotracheal aspirates (Table 1). Furthermore, impaired capacity to reduce surface tension has also been reported [21-23]. Taking methodological issues into account (such as method and timing of sampling), these studies suggest that shortage of surfactant lipids and impaired surfactant function play roles in the pathophysiology of viral LRTD. However, the actual pathophysiological mechanisms are unclear. Possible mechanisms include decreased production due to viral invasion of type II pneumocytes and altered regulation of the production of surfactant lipids. Furthermore, a protein overload in the alveoli could result in decreased surfactant function even when normal concentrations of surfactant lipids are present. Increased protein concentrations in BAL fluids have been observed in infants with viral LRTD [24]. In animal studies impaired capacity to reduce surface tension occurred when BAL fluid from RSV-infected BALB/c mice was added to calf lung surfactant extract [25]. The function of surfactant, determined using the capillary surfactometer, was impaired with increasing virus titre and correlated negatively with protein concentration in BAL fluid.

Restoring surface tension reduction by exogenous surfactant

The observation of lower levels of surfactant phospholipids and impaired capacity to reduce surface tension in infants with viral LRTD has led to the hypothesis that exogenous surfactant might be beneficial in restoring airway patency and

Table 2

Results from trials of the efficacy of exogenous surfactant in mechanically ventilated children with viral lower respiratory tract disease

	Reference		
	[26]	[27]	[28]
Study population	20 children with bronchiolitis	40 children with bronchiolitis	19 infants with bronchiolitis
% RSV^+	20%	100%	100%
Surfactant preparation	Curosurf	Curosurf	Survanta
Dosage	50 mg/kg once	50 mg/kg once	100 mg/kg twice
Time of administration	Unknown	Unknown	t = 0 and t = 24 hours after PICU admission
Inclusion criteria	PaO_2/FiO_2 ratio <150 PIP >35 cmH_2O	PaO_2/FiO_2 <150 PIP >35 cmH_2O	Oxygenation index >5 Ventilation index >20
Clinical phenotype	Restrictive	Restrictive	Obstructive
Ventilatory strategy			
Mode of ventilation	Volume control	Volume control	Pressure control
Permissive hypercapnia (pH > 7.25)	No	Yes	Yes
Permissive hypoxaemia (PaO_2 >60 mmHg or SaO_2 >88%)	No	Yes	Yes
Manual ventilation before surfactant administration	Yes	Yes	No
Main outcome findings			
Duration of mechanical ventilation	Reduced	Reduced	Tendency toward reduction[a]
Duration of PICU stay	Reduced	Reduced	Tendency toward reduction[a]
Oxygenation	Increased PaO_2/FiO_2	Increased PaO_2/FiO_2	Decreased oxygenation index and alveolar–arterial oxygen gradient

[a]Study was not powered to detect significant differences. FiO_2, fractional inspired oxygen; PaO_2, arterial oxygen tension; PICU, paediatric intensive care unit; PIP, positive inspiratory pressure; RSV, respiratory syncytial virus; SaO_2, arterial oxygen saturation.

improving lung compliance. Three randomized clinical trials were conducted to investigate this hypothesis [26-28] (Table 2).

Tibby and coworkers [28] randomly assigned 19 infants with RSV-induced respiratory failure and moderate oxygenation impairment (oxygenation index >5) to receive 100 mg/kg Survanta® (Abbott Laboratories, Abbott Park, IL, USA; a bovine surfactant preparation that contains phospholipids and SP-B and SP-C) or placebo. Two doses of surfactant were administered, one at enrollment and one 24 hours later. Administration of exogenous surfactant prevented further pulmonary deterioration, as indicated by oxygenation index, alveolo–arterial oxygen gradient and ventilation index. Although the study was not designed to detect differences in duration of mechanical ventilation, surfactant-treated infants were ventilated for significantly shorter periods than were nontreated infants (126 hours versus 170 hours). Interestingly, infants with an obstructive disease pattern were also included. They also appeared to benefit from exogenous surfactant.

Additional evidence came from two randomized trials conducted by Luchetti and coworkers [26,27]. Children aged 2 months to 2.5 years with virus (RSV)-induced respiratory failure with an arterial oxygen tension/fractional inspired oxygen ratio below 150 mmHg and a positive inspiratory pressure above 35 cmH_2O (indicating severe oxygenation disturbances) were randomly assigned to receive 50 mg/kg Curosurf (a porcine surfactant containing phospholipids as well as SP-B and SP-C) (Chiesi, Parma, Italy) once or nothing [26]. Children with an obstructive disease pattern were not included. In both studies a significantly higher arterial oxygen tension/fractional inspired oxygen ratio and lower positive inspiratory pressure was observed 24–48 hours after surfactant administration. More importantly, in both studies a significantly shorter duration of MV was observed among treated children (4.4 ± 0.4 days versus 8.9 ± 1.0 days in the first study [26] and 4.6 ± 0.8 versus 5.8 ± 0.7 days in the second study [27]) and intensive care unit stay (6.4 ± 0.9 days versus 8.2 ± 1.1 days in the control group) was noted.

These three studies suggest a beneficial role for exogenous surfactant in the treatment of viral LRTD when there is a reduced surface tension resulting in a decreased lung compliance with oxygenation disturbances. Compared with corticosteroids or the antiviral compound ribavirin, it seems at present that exogenous surfactant might be the only treatment modality that actually reduces duration of MV and paediatric intensive care unit stay [9]. However, the trials conducted by Luchetti and coworkers [26,27] have met with some criticism. Volume-controlled ventilation was used as a ventilatory strategy, but this may result in high inspiratory pressures in patients with small airway disease. Furthermore, in the first study by Luchetti and colleagues [26] there was no weaning protocol, large tidal volumes of 10 ml/kg were used and manual inflation before surfactant instillation was done, which itself could have induced beneficial effects.

Do these investigations provide sufficient evidence to justify the use of exogenous surfactant in mechanically ventilated infants with RSV LRTD? The three trials suggest that exogenous surfactant could be beneficial when there is impaired oxygenation, but we feel that the question cannot be answered until a properly designed, randomized controlled trial is undertaken. With respect to the costs associated with surfactant treatment in young children, it was recently demonstrated that exogenous surfactant is cost-effective [29].

Surfactant proteins and the host response against viruses

Various *in vitro* and animal studies have shown that SP-A and SP-D bind to respiratory viruses such as RSV, influenza virus, cytomegalovirus and herpes simplex virus type 1 to function as opsonins or to mediate viral aggregation [30-37]. Since this binding is usually calcium dependent, the lectin domain is mostly involved. The exact role of SP-A and SP-D in eliminating respiratory viruses is unclear, although there is evidence suggesting a role for both proteins [30-32,38,39]. Enhanced phagocytosis of RSV by peripheral blood monocytes and U937 macrophages in a dose-dependent manner was seen *in vitro*, suggesting that SP-A enhances viral uptake by phagocytic cells [40]. Additional evidence was found in SP-A knockout mice, in which increased viral titres of RSV and influenza virus were found [41,42]. In BALB/c mice pulmonary RSV titres were nearly undetectable when they received recombinant SP-D intranasally 4 hours before inoculation with RSV [36]. The efficacy of viral neutralization may also be mediated by SP-A. In SP-A negative mice decreased killing function of alveolar macrophages and neutrophils was observed [41,42].

SP-A and SP-D can induce a proinflammatory response to RSV and influenza virus, although in SP-A knockout mice a proinflammatory response has also been noted, and so the precise role played by SP-A and SP-D is unclear [40-43]. Recruitment of inflammatory effector cells such as neutrophils appears also to be mediated by SP-A [31,32]. In contrast, however, increased neutrophil counts have also been found in BAL fluid from SP-A negative mice compared with control mice [41]. Because of this, it can only be concluded that the presently available data on the immunomodulatory function of SP-A and SP-D are conflicting and that further study is warranted.

Surfactant protein deficiencies in childen with viral lower respiratory tract disease

Lower concentrations of SP-A and D have been described in young children with viral LRTD (Table 1) [21,22,24]. Possible explanations include decreased production of surfactant proteins due to viral invasion of type II pneumocytes and altered regulation of the production of surfactant proteins by inflammatory mediators. On the other hand, because SP-A and SP-D play a role in the host response to viruses, binding of the SPs with these viruses with subsequent phagocytosis might also explain why low concentrations of SPs are found. Furthermore, as in any other pulmonary inflammatory disease, the alveolar–capillary membrane gets disrupted and proteins could leak into the capillary system. Evidence for this was found in 15 young, previously healthy infants (aged 1–14 months) with acute bronchiolitis due to RSV, in whom increased plasma concentrations of SP-B (4017 ± 852 ng/ml versus 1313 ± 104 ng/ml in the control group), but not of SP-A, were found in comparison with healthy age-matched control infants [44]. However, none of the studied infants required MV, thus representing a less severe disease patient category. A possible explanation for the inability to detect SP-A in plasma may be its size, because SP-A is larger than SP-B, although the actual molecular weight of SP-A depends upon its glycosylation [45]. However, interpretation of SP concentrations in whole blood is also hampered by the fact that these proteins are produced throughout the body, rather than only being produced in the lungs [20].

It is interesting that lower concentrations of SPs have been observed also to result from genetic polymorphisms in the genes that encode these proteins. SP-A is encoded by two genes (*SP-A1* and *SP-A2*), which are located on chromosome 10 [46]. The gene encoding SP-D is also located on chromosome 10, near the locus of SP-A [47]. Human SP-A consists of assembled gene products of either one or both genes. The genes encoding SP-A and SP-D contain several single polymorphic sites that result in amino acid substitution. The haplotypes for the *SP-A1* gene have been denoted $6A^n$, whereas for *SP-A2* they have been denoted $1A^n$. More than 30 allelic variants have been described and are reviewed elsewhere [17,48]. Several alleles that differ by a single nucleotide have been characterized for both *SP-A1* and *SP-A2*. Similar to SP-A, allelic variants have been described for SP-D [47]. These polymorphisms in the SP-A and SP-D genes may contribute to disease severity. Löfgren and coworkers [49] found an overexpression of allele $1A^3$ of the *SP-A2* gene and

haploptype 6A/1A[3] in RSV-infected infants, whereas allele 1A of *SP-A2* and allele 6A of *SP-A1* were underrepresented. In the *SP-A2* gene lysine was found significantly more often at amino acid position 223, and proline significantly less at amino acid position 91 compared with controls. For SP-D it was found that a methionine–threonine substitution at position 11 was associated with a more severe RSV infection (i.e. necessitating hospitalization) [50].

Conclusion

Treating mechanically ventilated infants with viral LRTD remains a challenge. The common appreciation of surfactant being a substance that could only reduce surface tension in the lungs has changed because of increasing knowledge of the influence of SPs on host defence. Studies in mechanically ventilated children with viral LRTD have shown lower levels of surfactant phospholipids and impaired capacity to reduce surface tension, indicating a deficient pulmonary surfactant system. These studies have also demonstrated lower concentrations of SP-A and SP-D in these children. Data from *in vitro* and animal studies show that both proteins bind to respiratory viruses, play a role in the elimination of the viruses and induce an immune response. However, the data are not conclusive and not (yet) confirmed in human studies. Thus, exogenous surfactant in ventilated infants with viral LRTD could be a useful therapeutic approach. Its potential beneficial role in improving oxygenation has been established in clinical trials, although a well designed randomized controlled trial is eagerly awaited. Additionally, the immunomodulating effects are promising but remain to be elucidated.

Competing interests

The author(s) declare that they have no competing interests.

Author's contributions

All authors contributed equally to the writing of the manuscript.

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