Journal of Pediatric Intensive Care 2 (2012) 49–60
DOI 10.3233/PIC-2012-011
IOS Press

Review Article

Exogenous surfactant in the treatment of neonatal meconium aspiration syndrome

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Received 25 October 2010
Revised 30 January 2011
Accepted 11 February 2011

Abstract. Dysfunction of pulmonary surfactant is one of the key pathogenic features in meconium aspiration syndrome. Surfactant function may be affected by components of meconium, by inflammatory mediators (e.g., tumor necrosis factor alpha and interleukin-1), proteolytic enzymes, phospholipase A2, reactive oxygen species, and by plasma proteins leaking into the alveolar space. Administration of exogenous surfactant may at least partially alleviate the inactivation of pulmonary surfactant present in meconium aspiration syndrome. In experimental and clinical studies, intratracheal administration of a surfactant bolus significantly improved both lung function and survival. However, some patients are non-responders and there is only transient improvement in oxygenation. A repeat dose of surfactant may be required in these patients. Bronchoalveolar lavage with diluted exogenous surfactant is another technique for surfactant administration that may be more effective in partially removing meconium from the lungs, and thereby reducing surfactant inhibition, inflammation and mechanical obstruction of the airways. There is also a growing body of evidence suggesting that exogenous surfactant may be more effective when combined with pulmonary vasodilators, anti-inflammatory and antioxidant treatment.

Keywords: Surfactant, meconium aspiration, newborns, animal models

1. Meconium aspiration syndrome (MAS)

MAS is a severe respiratory disorder in the term and post-term neonate. Following aspiration of meconium, the airways become obstructed. Complete airway obstruction leads to alveolar atelectasis, and partial obstruction of the airways may cause a ball-valve effect, with subsequent air-trapping and air leak into the interstitium [1,2]. With initiation of mechanical ventilation, meconium moves distally, reaches the alveoli, causing both inactivation of pulmonary surfactant and an inflammatory response [3,4].

Meconium increases the number of neutrophils in the lungs within several hours after the aspiration [5,6]. In addition, meconium itself contains pro-inflammatory mediators, such as interleukin-1 (IL-1), IL-6, and IL-8, tumor necrosis factor alpha (TNF-α) [7], and bioactive substances such as phospholipase A2 [8]. Meconium also enhances the expression of inducible cyclooxygenase-2 and inducible nitric oxide synthase in the macrophages, epithelial and endothelial cells [9,10]. These mechanisms all contribute to both direct and indirect inflammation through the stimulation of cytokine release and oxidative burst in neutrophils [11] and alveolar macrophages [12]. Activated cells (leukocytes, platelets, epithelial and endothelial cells etc.) produce a number of substances like TNF-α, IL, leukotrienes, prostaglandins, platelet activating factor, proteolytic enzymes, and reactive oxygen and nitrogen species

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(RONS), which injure the lung parenchyma and inactivate surfactant [13]. Substances released during inflammation then induce expression of angiotensin II, which may cause apoptosis of the lung cells [14]. Subsequently, fluid and cells leak into the alveolar space through the alveolo-capillary membrane and contribute to further deterioration in lung function.

Meconium aspiration is also often associated with pulmonary vasoconstriction from hypoxia and/or from substances present in meconium (e.g. bile acids) and substances released during the inflammatory response [15–17].

2. Treatment of MAS

Since the pathophysiology of MAS is complex, it is often difficult to treat. Over the past several decades, various therapies have been tested in MAS, and surfactant administration represents one of the well accepted therapeutic options. As surfactant dysfunction plays an important role in the pathogenesis of MAS, administration of exogenous surfactant has become a method of choice in the treatment of severe MAS. This article will review the rationale for surfactant replacement therapy in MAS, surfactant composition and function, as well as experimental and clinical experiences with administration of exogenous surfactant in MAS.

3. Pulmonary surfactant

3.1. Composition of pulmonary surfactant

Synthesis of pulmonary surfactant is synthesized during the 30th–32nd week of gestationin type II pneumocytes. During breathing, surfactant is released into the alveoli. Surfactant then changes to tubular myelin and forms a thin film at the alveolar surface [18].

Pulmonary surfactant is a complex of phospholipids (PLs) (80% of the content), neutral lipids, proteins, and saccharides [18]. PLs are surface active, for example, dipalmitoylphosphatidylcholine reduces the surface tension at air: liquid interphase, while phosphatidylglycerol facilitates spreading of surfactant on internal surface of alveoli and terminal bronchioles [19]. Four native specific surfactant proteins (SP) have been identified. Hydrophilic proteins SP-A and SP-D play a role in the immune response to microbial challenge. In addition, SP-A regulates the secretion of surfactant and formation of surfactant aggregates including tubular myelin. SP-D is important in surfactant reuptake and recycling [20,21]. Hydrophobic proteins SP-B and SP-C promote formation and stabilization of surfactant film. SP-A and SP-B facilitate formation of tubular myelin, a precursor for the surfactant film [22,23].

3.2. Functions of surfactant

Surfactant stabilizes the alveoli and terminal airways. This stabilization by surfactant reduces work needed to open the lungs during inspiration and prevents collapse of the peripheral airspaces at the end of expiration [24]. Surfactant maintains a low surface tension, which decreases suction force into the alveoli and decreases leak of liquid from capillaries into the interstitium and alveolar space [25]. Surfactant also participates in protection and defense mechanisms of the lungs [18]. It decreases surface tension of bacterial membranes, protects epithelium from adhesion of microbes, increases activity of alveolar macrophages [26,27], reduces production of IL-1, IL-6, TNF-α, reactive oxygen species and metabolites of arachidonic acid [28,29]. As surfactant is partially squeezed out into the airways in each expiration, it stabilizes the weak wall of the terminal airways and enhances removal of inhaled particles and senescent cells outside the alveolar compartment [30,31].

3.3. Dysfunction of surfactant in MAS

Pulmonary surfactant may be inhibited by meconium components as well as by plasma proteins leaking through the injured alveolo-capillary membrane [32]. Several *in vitro* studies have demonstrated that meconium changes the viscosity and ultrastructure of surfactant. This change lowers the ability of surfactant to spread and reduces surfactant adsorption from hypophase to alveolar surface [3,33–35]. In meconium-instilled animals, time-dependent qualitative decrease in surfactant protein SP-A, but particularly in SP-B in the large aggregate fraction of surfactant was observed [36], probably due to decreased secretion and/or increased degradation.

Although both fractions of meconium may inhibit surfactant function and their action is additive, hydrophobic fraction possesses about 10-times stronger effect on surfactant than the hydrophilic one [3]. An extent of surfactant dysfunction is dependent on

concentration of both meconium and surfactant. Thus, in low concentration of surfactant even low concentrations of meconium can inhibit surfactant function. In contrast, surface properties of surfactant in high concentration may remain intact despite addition of concentrated meconium. Administration of exogenous surfactant increases intraalveolar pool of surfactant components as well as the surfactant: inhibitor ratio, thus, reducing inhibition by meconium [32].

Surfactant may be inactivated also by accelerated conversion of its structural forms [37]. Synthesized surfactant enters the alveoli in the form of 'large', highly surface active aggregates (large aggregates, [LA]). Due to cyclic changes of alveolar surface area during breathing, LA are converted to 'small', less active forms (small aggregates [SA]) [38]. In meconium-instilled animals, mechanical ventilation at high pressures and large tidal volumes speed up the conversion of surfactant subtypes to less active forms [39].

Besides meconium, surfactant may also be inactivated by pro-inflammatory mediators, RONS and proteolytic enzymes released from activated cells during inflammation as well as by plasma proteins leaking into the alveolar space. TNF-α and IL-1 also inhibit expression of SP [40]. Reactive oxygen species deteriorate particularly the function of surfactant PLs [41], reduce energetic pool in pneumocytes type II and synthesis of surfactant in *in vitro* conditions [42]. Proteolytic enzymes and phospholipases are able to break structure and function of surfactant [43]. Plasma proteins have different capacities to inactivate surfactant: fibrin monomer is the strongest inhibitor, followed by fibrinogen, albumin, and gamaglobulin [44]. In addition, meconium concentrations higher than 1% have direct toxic effect on pneumocytes type II [45]. Mechanisms of surfactant inactivation are summarized in Table 1. This knowledge affords the rationale for surfactant replacement therapy in MAS.

Table 1
Mechanisms of surfactant inactivation

Inhibitors of surfactant	Mechanisms of surfactant dysfunction
Components of meconium	Changes in ultrastructure
Plasma proteins	Changes in surface activity
Pro-inflammatory mediators	Changes in surfactant protein concentrations
Enzymes	Accelerated conversion of aggregates
Reactive oxygen and nitrogen species	

4. Exogenous surfactant in MAS

4.1. Exogenous surfactants

Exogenous surfactants may be extracted from natural sources (minced lung tissue or lung lavage fluid) or can be produced artificially.

Natural and modified natural surfactants of bovine (e.g. alveofact, surfacten, Survanta) or porcine (e.g. Curosurf) origin consist of phospholipid mixture, mostly of dipalmitoylphosphatidylcholine and phosphatidylglycerol, plus a small amount of SP (SP-B and/or SP-C). Synthetic surfactants traditionally contained only PLs (such as ALEC or Exosurf), but 'new' or third-generation surfactants are supplemented with agents which promote adsorption and spreading [20,46].

Natural and modified natural exogenous surfactants are more efficient in lowering surface tension and modulating inflammation than synthetic surfactants, and this attribute is likely related to the presence of SP in natural surfactants [47–50]. However, these surfactants are expensive and their supply is limited. Therefore, there is a need for synthetic surfactant substitutes, which can be produced in large quantities at a much lower cost [51]. Newly developed synthetic surfactants enriched with SP [52–54] and/or calcium [51] have improved surface properties, and their resistance to inactivation might be comparable with the natural surfactants. On the other hand, there is an intention to improve already existing surfactant preparations. Addition of ferric chloride, copper chloride, and acetic acid in *in vitro* conditions reversed surfactant inhibition by meconium, probably by lowering pH [55]. Enrichment of surfactant with polymyxin B [56,57], non-ionic polymers dextran and polyethylene glycol [58–60], and ionic polymers like hyaluronan [61] increased resistance to meconium and plasma inhibitors in *in vitro* measurements [56,57,59], and improved the lung functions also in meconium-injured rats [56,60, 61]. Addition of dextran to surfactant bolus after the lung lavage with diluted surfactant [62] or to surfactant lung lavage fluid [63] potentiated the therapeutic effects of surfactant in animals with MAS.

4.2. Administration of exogenous surfactant

Cochrane reviews of surfactant for neonatal respiratory distress syndrome demonstrate the benefits of: 1) multiple doses of surfactant over a single dose, 2) early (< 2 hr) versus delayed selective treatment,

3) prophylaxis versus selective use, and 4) natural versus "old" synthetic surfactant [64–67].

Generally, administration of exogenous surfactant increases a surfactant pool in the alveoli, increases a ratio between surfactant and inhibitors, stabilizes peripheral airspaces and facilitates the synthesis of endogenous surfactant [3,18]. Due to reduced atelactasis and more homogenous distribution of ventilation, exogenous surfactant enlarges the diffusion area and functional residual capacity of the lung. Surfactant changes local lung compliance, leading to redistribution of the blood flow into the lung regions [68]. This redistribution of blood flow, together with improved oxygenation, reduces both pulmonary vascular resistance and shunting through the fetal circulation channels [69]. Exogenous surfactant also prevents lung edema formation, decreases infiltration of the lungs by polymorphonuclear cells [70], production of RONS, nitric oxide, phospholipase A_2, arachidonic acid metabolites, and cytokines [48,50,71–77], reduces apoptosis [78] and thereby diminishes the lung injury. As a result, surfactant administration reduces ventilatory pressures and fraction of inspired oxygen and shortens duration of oxygen therapy. This may decrease an incidence of pneumothorax, periventricular bleeding, bronchopulmonary dysplasia, retinopathy and other complications.

Effects of exogenous surfactant on gas exchange and hemodynamic parameters depend on the type of surfactant as well as on the mode of delivery [69]. In the treatment of respiratory distress syndrome, surfactants have been administered by intratracheal instillation after short intubation followed by extubation to continuous positive airway pressure [20,79–81]. In the management of MAS, two modes of surfactant delivery have been used: administration of surfactant as a bolus and bronchoalveolar lavage with diluted surfactant.

4.3. Surfactant bolus in MAS

Intratracheal administration of surfactant improves oxygenation, lung compliance and mean airway pressure, and reduces atelectasis, lung edema, and hyaline membranes in experimental animals with MAS [82–84]. Similarly, in most newborns with MAS, surfactant instillation improved oxygenation, ventilatory pressures, and survival [85–90]. In some non-responders, the improvement in oxygenation was transient, and in these circumstances, repeated doses of surfactant are often administered [87–89] (Table 2).

Although exogenous surfactant is well tolerated by majority of newborns, bolus administration may have consequences on hemodynamics [91,92]). Adverse effects of surfactant administration are related to rapid improvement in oxygenation and subsequent decrease in pulmonary vascular resistance. These physiologic changes increase left-to-right shunting and may lead to a precipitous drop in cardiac output and systemic arterial blood pressure. These hemodynamic changes may increase cerebral blood flow velocity, cause abnormalities on electroencephalography and increase the risk of intraventricular bleeding [69,93]. Benefits and risks of surfactant administration in MAS are depicted in Table 3 [46]. Questionable effectiveness and higher risk of complications related to instillation of surfactant as a bolus dose [69,94–96] have led to a search for additional, more homogenous, and safe ways to administer surfactant. Alternative administration strategies include the use of surfactant bolus divided into several portions [97], slow tracheal infusion [98], nebulization [99], instillation by means of asymmetric high-frequency jet ventilation [100], or lung lavage with diluted surfactant [101–105].

4.4. Surfactant lung lavage in MAS

As shown in experimental models of MAS [101–105], bronchoalveolar lavage with diluted surfactant is a promising alternative to surfactant bolus administration. Higher volume of lavage fluid improves the distribution of surfactant throughout the lungs [106] and allows dose reduction without influencing efficacy of the treatment [107,108]. In addition, surfactant lavage removes aspirated material from the lungs [103,104, 109] by reducing surface tension of highly viscous meconium [110] and increasing mucociliary transport [111]. Removal of meconium from the lungs may be further potentiated by the expulsion effect of high-frequency jet ventilation [112], and/or by fortification of surfactant by substances influencing surface properties of meconium, such as dextran [63]. Partial removal of meconium reduces mechanical obstruction of the airways and improves distribution of the following dose of lavage fluid. Stabilization of the alveoli and small airways leads to better distribution of ventilation and more effective gas exchange [101,103,104]. Enhanced aeration of the lungs increases lung compliance and reduces right-to-left pulmonary shunts [102–112].

Table 2
Clinical trials of surfactant bolus administration in meconium aspiration syndrome

Study (Year) (Ref. no)	Study groups	Surfactant dose	Administration	Repeated dosing	Positive effects of therapy	Adverse effects of therapy
Auten et al. (1991) [85]	Seven infants	Calfactant, 90 mg/kg			Improved oxygenation decreased: mean airway pressure	Not described
Khammash et al. (1993) [86]	20 infants	Bovine lung extract surfactant, 100 mg/kg			Improved oxygenation in 75% of infants	Not described
Halliday et al. (1996) [87]	54 infants	Poractant alpha, initial dose 50–200 mg/kg	Median age 14 h	Repeated dose required 33% of infants	Slightly improved oxygenation	44% of non-responders
Findlay et al. (1996) [88]	Randomized study; 20 surfactant-treated infants, 20 controls	Beractant, 150 mg/kg	<6 h after delivery, infusion via endotracheal tube sideport over 20 min	Up to four doses 6 h apart	Improved oxygenation, decreased : mean airway pressure, reduced risk of air leak, reduced need for extracorporeal membrane oxygenation, shorter duration of mechanical ventilation, oxygen therapy and admission	Not described
Lotze et al. (1998) [89]	Randomized study; 87 surfactant-treated infants, 81 controls	Beractant, 100 mg/kg	Mean age 31 h after delivery, small boluses via endotracheal tube side port	Up to four doses 6 h apart	Reduced need for extracorporeal membrane oxygenation	Hypoxia, obstruction of endotracheal tube and bradycardia during administration
Chinese Group (2005) [90]	Randomized study; 31 surfactant-treated, 30 controls	Poractant alpha, initial dose 200 mg/mL	Intratracheally by feeding tube	Four doses (200, 200, 100 and 100 mg/mL) at 6–12 h intervals	Trend to improved oxygenation	Not described

Table 3
Recommendations for surfactant bolus administration by Dargaville and Mills [46]

Recommendations for surfactant bolus administration in meconium aspiration syndrome
– Administer surfactant selectively in newborns with severe meconium aspiration syndrome associated with pulmonary hypertension, with oxygenation index > 15 and/or alveolar-arterial oxygen difference > 450 mmHg
– If necessary, begin surfactant administration as early as possible (< 6 h after delivery), after intubation and stabilization of the newborn
– Due to higher resistance to inactivation prefer natural or "third-generation" synthetic surfactants
– Divide the dose of surfactant (100 mg phospholipids/kg) into several portions and administer gradually into the trachea
– If oxygenation remains compromised, use repeated doses every 6 h

In majority of newborns with MAS, surfactant lung lavage improved oxygenation, reduced requirements for oxygen supplementation, and shortened the period of hospitalization. In addition, this procedure was tolerated well without serious adverse effects by most newborns [113–121]. Nevertheless, effectiveness of surfactant lung lavage particularly in large randomized trials [116,118,122] was less definitive than would have been expected based on prior studies. As previously discussed by Kinsella [123], clinical MAS is considerably more complex than models created by meconium instillation into the airways of healthy several-week-old animals. Clinical MAS may involve multisystem organ failure, abnormal muscularization of the smallest intraacinar arteries associated with pulmonary hypertension and extrapulmonary right-to-left shunting, all of which may increase the risks associated with aggressive lung lavage in the early stages of the disease [123]. Although most clinical trials showed no significant adverse effects of surfactant lung lavage, large-volume lung lavage in neonates with severe MAS may be associated with transient hypoxemia, rarely with bradycardia, systemic hypotension or other cardiovascular disturbance [46, 116,123]. To avoid cardiovascular perturbations and aggravation of the newborn state, potential risks and benefits of surfactant lung lavage should be carefully considered. Nevertheless, definitive recommendations including information on the safety and efficiency of surfactant lung lavage depends on the conclusions of multicenter randomized trials that are currently underway [122].

Within the last two decades, different volumes, surfactant concentrations and procedures have been tested in the treatment of MAS (Table 4). Concentrations of PLs have varied between 2.5–12 mg of PL per ml of the lavage fluid [46]. However, most of investigators used PL concentration of 5 mg/mL, that had been shown as sufficiently resistant to inactivation by meconium or plasma inhibitors [3,32,124]. Total volumes of lavage fluid have ranged from 5 to 80 mL/kg body weight in experimental models, and these doses have been divided into portions of 2–15 ml/kg. In newborns with MAS the total volumes range from 3–48 mL/kg, divided into portions of 1–15 ml/kg [46].

However, in recent clinical studies, two modes of delivery (small-volume vs. large-volume) of surfactant diluted to a concentration of 5 mg PL per ml have been performed. Small-volume approach uses a total volume of 15 ml/kg divided into eight portions of 2.5 ml [125]. The large-volume technique is performed during positioning of the newborn with a total volume of 30 ml/kg divided into two portions of 15 ml/kg [120,121]. In addition, positive effects of the lung lavage by diluted surfactant on the lung functions may be further potentiated by administration of undiluted surfactant bolus after the lavage [115,119].

The recovery of the surfactant lavage fluid in meconium-instilled animals varies between 30–75% [46,112, 126]. Incomplete recovery of the lavage fluid may contribute to fluid retention in the lungs, however, benefits from meconium removal likely outweigh the potential adverse effects from intratracheal fluid instillation. Lavage with large-volume aliquots of 15 mL/kg is not only an effective means for clearing meconium from the lungs, but it is also associated with less fluid deposition in the lungs [109]. Similar results have been found in a recent experimental study in which lavage with total volumes of 20 ml/kg and 30 ml/kg divided into two aliquots was more effective in improvement in lung function than small-volume lavage [127].

4.5. Surfactant bolus vs. lung lavage

Lung lavage by surfactant replaces the surfactant inactivated by meconium, plasma proteins and the inhibitors originated from the lungs due to meconium-induced inflammation. In addition, lung lavage removes considerable portion of meconium and debris and thereby improves lung function. For lung clearance, large-volume

Table 4
Clinical trials of surfactant lung lavage in meconium aspiration syndrome

Study (Year) (Ref. no)	Study groups	Surfactant	Lavage fluid concentration	Total lavage volume/ Aliquot volume	Lavage fluid administration	Effects of therapy
Ogawa et al. (1997) [113]	Randomized study; six surfactant-lavaged infants, six saline-lavaged controls	Surfacten	6 mg/mL	10 mg/mL/2 mL/kg	<12 h	Improved oxygenation and ventilation
Lam and Yeung (1999) [114]	Six lavaged infants, six controls	Beractant	5 mg/mL	15 mL/kg/2 mL	3 h after delivery	Improved oxygenation, decreased mean airway pressure, reduced duration of ventilation and oxygen therapy
Kaneko et al. (2001) [115]	Two lavaged infants	Surfacten	12 mg/mL	3 mL/kg/1 mL	3 respectively 2 h after delivery; surfactant bolus 40 mg/kg after the lavage	Improved oxygenation
Wiswell et al. (2002) [116]	Randomized study; 15 lavaged infants, seven controls	Lucinactant	4-times 2.5 mg/mL followed by 2-times 10 mg/mL	48 mL/kg/8 mL/kg	14 ± 12 h after delivery	Trend to improved oxygenation
Schlösser et al. (2002) [117]	11 lavaged infants, seven controls	Beractant	5 mg/mL	20 mL/kg/5 mL/kg	Not stated	Improved oxygenation
Chang et al. (2003) [118]	Six low-volume lavaged, six high-volume lavaged infants, 10 controls	Beractant	10 mg/mL (low-volume) respectively 5 mg/mL (high-volume)	6–7 mL/kg/2 mL (low-volume) respectively 12–14 mL/kg/2 mL (high-volume)	4 respectively 5 h after delivery	Trend to improved oxygenation in both regimen vs. controls
Szymankiewicz et al. (2004) [119]	Seven lavaged infants, nine controls	Beractant	5 mg/mL	15 mL/kg/3.75 mL/kg	5 h after delivery	Improved lung compliance and resistance
Dargaville et al. (2007) [120]	8 + 3 lavaged infants, 34 controls	Beractant	5 mg/mL	30 mL/kg/15 mL/kg	Median age 23 h after delivery	Improved oxygenation and mean airway pressure
Lo et al. (2008) [121]	Three infants	Beractant	5 mg/mL	30 mL/kg/15 mL/kg	<24 h of age	Improved outcome

lavage has been shown to be more effective than bolus administration [109,127].

In contrast, regarding the potential hemodynamic complications associated with lung lavage, some authors recommend the early use of exogenous surfactant administered as small volume boluses as an approach in severe MAS [90,123]. This opinion has been recently supported by Gadzinowski et al. [128], who compared efficacy of surfactant treatment either by bolus or lung lavage in infants with MAS and persistent pulmonary hypertension of the newborn. The authors found no advantage of lung lavage therapy over bolus surfactant treatment [128]. Thus, further clinical investigations are necessary until any consensus on appropriate surfactant administration can be made.

5. Potential treatment options

Regardless of bolus or lung lavage administration, development of synthetic surfactants able to reduce surface tension, suppress inflammation, and resist inactivation more effectively is warranted [79]. In a recent study, instillation of recombinant SP-C-based surfactant into the trachea of newborn piglets with MAS led to comparable improvement in lung function, gas exchange, and pulmonary ultrastructure as natural surfactant [75]. In another model of MAS, administration of recombinant human Clara cell (CC) protein 10 (rhCC10) significantly decreased TNF-α levels at 24 hours compared with saline controls [129].

Combination of surfactant preparations with other drugs may further amplify efficiency of the therapy. Exogenous surfactant has been increasingly used as a carrier for drug administration directly into the lungs. Thereby, administered drugs, such as antibiotics and antiviral agents [130–132], vasodilators [133], glucocorticoids [134–137] or immunosuppressants [138] may act locally with minimum systemic adverse effects. In animal models of acute lung injury, local administration of anti-inflammatory drugs, such as 5-lipooxygenase inhibitor [139], NF-kappaB inhibitor [140] or sphingomyelinase inhibitor imipramine [141] using surfactant as a carrier improved lung function more effectively than surfactant alone. However, the value of these findings in the setting of MAS has yet to be tested.

In conclusion, experimental and clinical studies on the effects of exogenous surfactant in MAS have shown that surfactant administered as bolus or lung lavage may improve lung function. Nevertheless, existing evidence does not justify the use of surfactant as a primary treatment in MAS. While surfactant bolus administration is used sporadically, surfactant lavage continues to be an experimental therapy. Thus, because of complex pathophysiology of MAS involving both alveolar atelectasis and persistent pulmonary hypertension of the newborn, bolus surfactant therapy may be considered as suitable adjunct therapy in addition to standard ventilatory support and pulmonary vasodilators.

Acknowledgements

Supported by Project "Center of Excellence for Perinatology Research" No. 26220120016, co-financed from EU sources, and by Grant of Ministry of Education VEGA No. 1/0061/08.

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