

Recent Clinical Trials of Surfactant Treatment for Neonates

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Key Words

Neonate · Respiratory distress syndrome · Meconium aspiration syndrome · Clinical trials · Systematic reviews · Surfactants

Abstract

Objective: To search for recent clinical trials of neonatal surfactant treatment and report their findings. **Methods:** Recent was defined as published between 2000 and 2005. An online search on PubMed was made on 30th December 2005 using the following terms: surfactant treatment, clinical trials and neonate, with limits of years 2000 to 2005 and age – newborn from birth to 1 month. Randomised clinical trials (RCTs) and systematic reviews of RCTs were prioritised and studies in children and animals were excluded from further analysis. **Results:** 175 papers were found in this search. Only about half of these papers were directly related to some aspect of surfactant treatment and of these just over one-half were either RCTs or systematic reviews of RCTs. Of the 34 RCTs of surfactant treatment, 3 were excluded as they involved children or animals rather than neonates. Twenty-nine trials studied preterm babies with respiratory distress syndrome (RDS) and 2 were for meconium aspiration syndrome (MAS) in term infants. The median sample sizes of these studies were RDS (92, range 19–1,361) and MAS (42, range 22–61). Eighteen of the RDS trials com-

pared two or more surfactant preparations, the most frequently studied being Curosurf and Survanta but altogether 11 different surfactants were compared. These new RCTs need to be analysed by meta-analyses in systematic reviews. Twelve systematic reviews were found and these demonstrated the superiority of prophylactic over selective use of surfactant in babies <30 weeks, natural over synthetic surfactant and the absence of an increase in long-term developmental sequelae. Surfactant for MAS may reduce the severity of respiratory illness and the need for extracorporeal membrane oxygenation. Of the non-randomised trials' novel delivery methods, failure to use evidence-based guidelines and the benefit of surfactant for babies <25 weeks were the most interesting. **Conclusions:** Surfactant remains one of the most effective and safest interventions in neonatology. Prophylactic natural surfactant seems to be the most evidence-based treatment for babies <30 weeks. Of the newer synthetic surfactants, only Surfaxin has been compared with currently used surfactants and systematic reviews are needed to establish if it has a role in treatment of RDS. The improvement in outcome for babies <25 weeks has been due to a number of interventions: prenatal steroids, prenatal antibiotics and postnatal surfactant. Clinical trials of surfactant replacement in the neonate continue to be published with remarkable frequency.

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Introduction

The first report of successful treatment of respiratory distress syndrome (RDS) with surfactant in preterm infants was in 1980 [1]. Since then many surfactant preparations, both synthetic and natural, have been licensed for clinical use following many large randomised clinical trials summarised in a recent review [2]. Clear benefits of surfactant treatment are a reduction in neonatal mortality and pneumothorax. Most of the trials were performed in the 1980s and 1990s and the systematic reviews in the Cochrane Library are based mainly on trials conducted before 2000 [2, 3].

Surfactant has also been used to treat other pulmonary disorders in the neonate, most notably meconium aspiration syndrome (MAS), but the evidence for significant long-term benefit is sparse [4]. The aim of this review was to search for recent clinical trials of surfactant treatment for any neonatal indication and to discuss their findings. For the purposes of this review, trials reported from 2000 were defined as recent.

Methods

Recent clinical trials of surfactant treatment in neonates were searched for online in PubMed on 30th December 2005 using the following terms: surfactant treatment and clinical trials and neonate, with limits of years 2000–2005 and age – newborn from birth to 1 month. The trials had to be in humans rather than animals and those of most interest were randomised controlled trials (RCTs) and systematic reviews of RCTs. Trials were grouped according to the indication for surfactant treatment and the type of surfactant

used. Comparative trials of various surfactants were assembled separately. The surfactant preparations used in these trials are listed in table 1 which shows their proprietary and generic names.

Results

175 papers were found in PubMed using this search strategy. Just less than half of them were directly related to some aspect of surfactant treatment and just over one-half of these were either RCTs or systematic reviews of RCTs (fig. 1). One paper reported the results of 2 randomised trials comparing 2 bovine surfactant preparations [5].

The non-surfactant trials were less likely to be randomised (19 vs. 39%) but more likely to be either systematic reviews (19 vs. 14%) or other reviews (17 vs. 10%) when compared with the surfactant trials.

Of the 34 RCTs of surfactant treatment, 2 were in children rather than neonates and 1 was an animal experiment leaving 31 true neonatal RCTs (table 2). Twenty-nine of these trials studied preterm babies with RDS and 2 were for treatment of term babies with MAS. In general the studies were small although 3 enrolled over 1,000 infants. The median sample size of the RDS trials was 92 (range 19–1,361) and for the MAS trials 42 (range 22–61).

Eighteen of the RDS trials compared 2 or more surfactant preparations [5–21] (table 2). The most frequently used surfactant was Curosurf followed by Survanta. Ten of the studies were performed in the USA, 3 in the UK and 2 in Greece (table 2). Apart from 2 multinational

Table 1. Surfactant preparations and their source

Proprietary name	Generic name	Source	Producer	Country
ALEC	Pumactant	Synthetic	Britannia ¹	UK
Alveofact	Bovactant	Bovine	Thomae	Germany
bLES	BLES	Bovine	BLES Biochemicals	Canada
Curosurf	Poractant alfa	Porcine	Chiesi Farmaceutici	Italy
Exosurf	Colfosceril palmitate	Synthetic	GlaxoSmithKline	USA
Infasurf	Calfactant	Bovine	ONY Inc.	USA
Newfactan	Not known	Bovine	Not known	Korea
Surfacen	Not known	Porcine	Not known	Cuba
Surfacten	Surfactant-TA	Bovine	Tokyo Tanabe	Japan
Surfaxin	Lucinactant	Synthetic	Discovery Labs	USA
Survanta	Beractant	Bovine	Ross Labs	USA

¹ Pumactant is no longer being produced by Britannia.

studies in which Surfaxin was compared with other surfactants, studies were carried out in 15 different countries.

The 18 comparative studies are listed in table 3 [5–21]. Eleven different surfactant preparations were studied in these comparative trials: Infasurf, Survanta, Curosurf, Surfacen, Newfactan, Surfacten, Surfaxin, bLES, Alveofact, Exosurf and ALEC (table 1). The sample sizes were also relatively small (median 100, range 24–1,361). Survanta was compared with Curosurf and Alveofact with Survanta in 2 studies in each case whereas 3 studies each compared Curosurf with Exosurf, and Infasurf with Survanta. In 2 studies, 3 surfactants were compared. In 1 of these studies, Surfaxin was compared with Exosurf and this study had a reference arm of Survanta-treated infants. In another study, Surfaxin was compared with Curosurf. Most of these studies were treatment trials when surfactant was given to babies with established RDS in the neonatal unit (n = 15), 1 study was truly prophylactic as surfactant was given in the delivery suite within 10–15 min of birth and in 2 studies, although the surfactant was given in the delivery suite, this was between 20 and 30 min after birth (table 3).

From 2000 to 2005 there were 2 randomised trials of surfactants to treat MAS [22, 23]. In 1 small trial, Surfaxin was used in a dilute form to lavage the lungs of 15 babies with severe MAS [22] but although the authors claimed it to be a safe and potentially effective therapy there was a critical commentary from Kattwinkel [24]. Amongst other concerns he pointed out the large volumes of fluid required for repeated lavages and the 20% of subjects who had the procedure halted because of severe hypoxemia or hypotension. The second study used conventional repeated doses Curosurf in a RCT of 61 infants with severe MAS in China. There were modest improvements in oxygenation favouring the surfactant-treated group [23].

In the time period of this review there were 12 systematic reviews of clinical trials of surfactant treatment the most important of which demonstrated the superiority of prophylactic over selective use of surfactant in babies less than 30 weeks' gestation [25], superiority of natural (animal-derived) over synthetic (protein-free) surfactant for RDS [26] and the relative safety of surfactant treatment after 1–2 years of follow-up [27]. A systematic review of surfactant for MAS [4] which was conducted before the Chinese trial [23] had been published concluded that, whilst treatment may reduce the severity of respiratory illness and the need for extracorporeal membrane oxygenation (ECMO), further trials were needed.

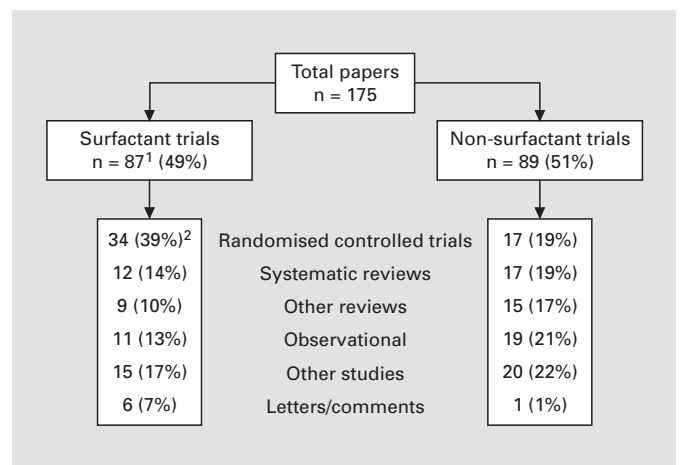


Fig. 1. Recent trials of surfactant treatment in neonates discovered after a PubMed search on 30th December 2005. ¹ One paper reported the results of 2 randomised trials. ² Two trials were in children rather than neonates and 1 study involved an animal model.

Table 2. Randomised controlled trials of surfactant treatment in neonates from 2000 to 2005 (n = 31)

	RDS (n = 29)	MAS (n = 2)
Sample size ¹	92 (19–1,361)	42 (22–61)
Type of surfactant		
Curosurf	5	1
Survanta	4	0
Surfaxin	0	1
Infasurf	1	0
Alveofact	1	0
Comparison trial	18	0
Country where studied		
USA	10	1
UK	3	0
Greece	2	0
China ²	1	1
Mexico	1	0
Korea	1	0
Turkey	1	0
Germany	1	0
Spain	1	0
Kuwait	1	0
Italy	1	0
Brazil	1	0
Czech Republic	1	0
Australia	1	0
Finland	1	0
Multinational	2	0

RDS = Respiratory distress syndrome; MAS = meconium aspiration syndrome.

¹ Median (range). ² Includes Hong Kong.

Table 3. Randomised trials comparing two or more surfactant preparations to treat RDS from 2000 to 2005 (n = 18)

Surfactants compared	Sample size	Timing min	Reference (first author and year)
Infasurf vs. Survanta	749	P	Bloom, 2005 [5]
Infasurf vs. Survanta	1,361	<2,160	Bloom, 2005 [5]
Survanta vs. Curosurf	58	T	Malloy, 2005 [6]
Survanta vs. Surfacten	44	T	Sanchez-Mendiola, 2005 [7]
Newfactan vs. Surfacten	492	T	Choi, 2005 [8]
Surfaxin vs. Curosurf	252	<30	Sinha, 2005 [9]
Surfaxin vs. Exosurf (vs. Survanta)	1,294	<30	Moya, 2005 [10]
Survanta vs. bLES	60	<360	Lam, 2005 [11]
Alveofact vs. Survanta	50	T	Yalaz, 2004 [12]
Alveofact vs. Survanta	109	T	Hammoud, 2004 [13]
Infasurf vs. Survanta	40	T	Attar, 2004 [14]
Survanta vs. Curosurf	296	T	Ramanathan, 2004 [15]
Survanta vs. Curosurf vs. Alveofact	79	T	Baroutis, 2003 [16]
Curosurf vs. Exosurf	50	T	Beresford, 2003 [17]
Alveofact vs. Exosurf	92	T	Giannakopoulou, 2002 [18]
Exosurf vs. Curosurf	24	T	Murdoch, 2000 [19]
Exosurf vs. Curosurf	228	T	Kukkonen, 2000 [20]
Curosurf vs. ALEC	212	<120	Ainsworth, 2000 [21]
Median (range)	100 (24–1,361)		

T = Treatment of RDS, time limit unknown; P = prophylaxis – surfactant given in delivery suite before 15 min of age; NS = not stated in abstract.

There were a few non-randomised trials of interest published between 2000 and 2005 and these included novel techniques for less invasive administration of surfactant both intrapartum [28] and in the neonatal unit [29]. The former used delivery of surfactant into the nasopharynx followed by continuous positive airway pressure (CPAP) and the latter a laryngeal mask to administer surfactant without the need to intubate the trachea. These techniques may be effective but large randomised clinical trials will be required to determine this with certainty. A previous trial of nebulised surfactant for babies on CPAP showed no apparent benefits and the authors concluded that their findings did not justify large clinical trials [30]. An important observational study from the Vermont Oxford Network concluded that the time after birth at which the first dose of surfactant was administered to infants of 23–29 weeks' gestation decreased from 1998 to 2000 [31]. However, many infants still received delayed treatment and delivery room surfactant administration was not routinely practised in most units. There was a gap between the evidence from RCTs that support prophylaxis or early surfactant treatment and what is actually done in routine clinical practice in many US neonatal units [31]. To

address this problem the same authors undertook a collaborative quality improvement initiative aimed at increasing evidence-based surfactant treatment of preterm infants of 23–29 weeks' gestation [32]. The intervention was tested in a cluster RCT in 114 neonatal intensive care units in the USA. The multifaceted intervention which included audit and feedback, evidence reviews, quality improvement training and follow-up support changed the behaviour of health professionals and promoted evidence-based practice with a 37% increase in surfactant treatment in the delivery room. The median time of administration of surfactant decreased from 78 to 21 min but contrary to the findings of an earlier systematic review [25] this did not lead to significant reductions in mortality or pneumothorax [32]. The power of the study was probably insufficient to demonstrate differences in these primary outcomes. However, there was a significant reduction in an important secondary outcome as severe intraventricular haemorrhage was reduced from 14 to 10% by earlier treatment with surfactant. This important finding had already been reported in a meta-analysis of 3 prophylaxis versus rescue treatment trials with Curosurf [33].

To address the question of whether surfactant treatment is effective in infants of <25 weeks' gestation, Hintz et al. [34] used the National Institute of Child Health and Human Development Neonatal Research Network database. They compared mortality and morbidity in the pre-surfactant era (1991–1994) with that in the post-surfactant era (1995–1998) and found that survival to hospital discharge was significantly more likely in the latter era because of group differences in the use of antenatal steroids, antenatal antibiotics and postnatal surfactant [34].

Using the results of a survey of fatal suspected adverse drug reactions received by the UK Committee on Safety of Medicines through its Yellow Card Scheme, Clarkson and Choonara [35] reported 13 deaths in association with a lung surfactant between 1992 and 1995. Pulmonary haemorrhage was reported as the cause for all but 1 of the babies, and in the remaining baby, cerebral haemorrhage was the reported cause. There were 6 reports for Exosurf and 7 for Survanta but the authors concluded that, although pulmonary haemorrhage is a recognised adverse drug reaction associated with surfactant therapy, the relative risk is small in comparison with the documented benefits of surfactant therapy [35].

Discussion

Although the first clinical trials with surfactants were conducted in the 1960s [36], the first successful report did not appear until 1980 when Fujiwara et al. [1] published the results of treatment of 10 preterm infants who had RDS with a bovine surfactant. Since then, following a number of RCTs, many surfactant preparations have been licensed to treat or prevent RDS in preterm newborns. They include synthetic surfactants (Exosurf and ALEC) and natural surfactants (Surfactant-TA, Survanta, Curosurf, Alveofact, Infasurf and bLES) used in various countries worldwide. Randomised trials and systematic reviews suggest that natural surfactants are superior to synthetic preparations [26, 37] with a significantly reduced risk of pneumothorax and neonatal mortality. Prior to 2000 there were 8 trials comparing natural and synthetic surfactants [26] and a small number of trials which compared different natural surfactant preparations. These have been summarised in a previous report [2]. However, there has been no formal meta-analysis of these trials apart from 2 short reports [2, 38]. There is a clear need for such a systematic review and this is endorsed by the results of this review which found 18 comparative

studies since 2000. These studies could easily be added to existing and new systematic reviews for publication in the Cochrane Library.

Furthermore there are now at least 2 randomised trials where a new synthetic surfactant containing a peptide analogue (Surfaxin) has been compared with other existing surfactants. This surfactant may be superior to protein-free surfactants such as Exosurf [10] but there is not much evidence to date that it is as good as or better than existing natural surfactant preparations [9, 10] for treatment of RDS. Indeed one commentator found problems with both studies which he said indicated that we may not yet have found the 'holy grail' [39]. Meta-analyses may be a means of determining whether or not this new synthetic surfactant behaves more like existing natural surfactants than existing synthetic surfactants.

In the period 2000–2005, further evidence emerged to support the use of prophylactic surfactant in the delivery room for very preterm infants rather than wait to use rescue treatment in the neonatal unit. The reduction in severe intraventricular haemorrhage found in both the meta-analysis of trials of Curosurf [33] and the cluster randomised trial from the Vermont Oxford Neonatal Network [32] underline the importance of very early treatment in preterm infants of <30 weeks' gestation. Quality improvement initiatives can encourage the use of evidence-based surfactant therapy [32] although unfortunately there is still much to do in this respect, particularly in the USA [31].

Most of the evidence points towards surfactant being an effective treatment for infants with gestational ages <25 weeks [34] but other interventions are also important to improve outcome for these very immature babies. Both prenatal antibiotics, especially if there is colonisation of the mother with group B streptococci or rupture of the membranes, and prenatal corticosteroids to help mature the fetal lung and reduce the risk of intraventricular haemorrhage, are important interventions in this regard.

The safety of surfactant treatment is well established in reviews of both short- and long-term outcomes. In 2002, Sinn et al. [27] reported a meta-analysis of neurodevelopmental outcome at 1 and 2 years of infants who had been treated in RCTs of neonatal surfactant therapy. They concluded that surfactant therapy increases survival without an increase in subsequent morbidity at 1 and 2 years of age. This is very reassuring but the report of Clarkson and Choonara [35] reminds us that pulmonary haemorrhage can still be a cause of death in surfactant-treated infants. In a previous meta-analysis it was shown

that the increased risk was mainly due to treatment with synthetic surfactant preparations and may have been related to development of a large persistent ductus arteriosus (PDA) [40]. Prophylactic use of surfactant and careful management to prevent a large PDA probably help to reduce the risk of pulmonary haemorrhage.

Treatment of MAS is not an established indication for surfactant therapy. Two trials published between 2000 and 2005 provide evidence of modest improvements in oxygenation without significant decrease in the need for assisted ventilation when surfactant is used to treat MAS

[22, 23]. Although theoretically attractive, lavage of the lungs with surfactant [22, 24] has not been shown to be better than repeated doses [23]. The use of surfactant in MAS may however reduce the need for ECMO but further trials are needed before surfactant can be recommended as a routine treatment for MAS [4].

In recent years, clinical trials of surfactant replacement in neonates continue to be published with regularity and they help to improve our understanding of this important therapy.

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