

Is There Evidence for a Mortality Difference Between Exogenous Surfactant Preparations in Neonatal RDS?

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ABSTRACT

Exogenous surfactants are effective in neonatal respiratory distress syndrome (RDS) because infants born preterm are partially surfactant deficient. While exogenous surfactant has significantly reduced the incidence of RDS-related deaths, no well-conducted, prospective, randomized comparison trial has shown a mortality difference. Claims that some exogenous preparations have shown a mortality benefit rely on 2 studies that were not designed to answer this question. Neither manufacturer of these surfactants has tried to reproduce this important benefit, if real, in rigorous clinical trials of adequate size and power. Based on what we have learned from surfactant research for the past 30 years, claims of differences in mortality for different surfactant preparations must be viewed with extreme caution.

INTRODUCTION

Recently a series of publications has been touted as evidence that mortality can be influenced by the choice of a surfactant for extremely premature babies treated prophylactically at birth (because of the risk of respiratory dis-

tress syndrome [RDS]) or babies treated after RDS has developed. However, it is not scientific evidence, but perhaps overzealous pharmaceutical marketing that purports “advantage.”

Lung surfactant is a complex, but not mysterious, material essential for lung functioning. In its active form it exists as a monomolecular film of lipids, primarily phospholipids, at the air-liquid interface of the lung. In expiration the surfactant molecules pack together so tightly that the surface tension normally generated at a liquid-gas interface shrinks to ~0 mN/m eliminating the atelectatic force at end expiration. In inspiration the molecules become less tightly packed as the surface of an alveolus expands, allowing surface tension to rise, thereby providing a critical force that prevents overexpansion (volutrauma) of some alveoli and under aeration of the rest. In a baby in respiratory difficulty because of inadequate endogenous lung surfactant, supplementing surfactant activity can be life saving. The only mechanism for benefit babies receive from lung surfactant treatment is an improvement in the function of the lung lining film. These agents have never

been shown to reduce the myriad of non-pulmonary complications of preterm birth; they are not magic potions.

Laboratory vs Clinical Differences

When several lung surfactants were placed into use in the United States in the 1990s, there were both commercial and scientific motivations to determine if there were significant differences in clinical responses. In the laboratory, compositional differences in these surfactants produced measurable variations in biophysical and biological properties. However, these differences were much less obvious in the clinical arena (which is not surprising) for several reasons. First, neonatal RDS is a partial, not a total, surfactant deficiency.¹ Laboratory studies often evaluated exogenous surfactants in the complete absence of endogenous activity. Second, although it is now recognized that the hydrophobic apoproteins SP-B and SP-C are required to create the lung lining film and for it to vary surface tension,² in most neonatal patients there is enough “extra” endogenous apoproteins SP-B/C to incorporate any exogenous phospholipids instilled into the lungs to significantly improve the function of the lining film.³ Thus even exogenous surfactants without any apoproteins diminish the mortality and mitigate the severity of RDS.⁴⁻⁶

No Evidence of Mortality Differences in Several Large Clinical Trials

Comparing Synthetic to Natural Surfactants

Four large (several hundred in each group), prospective randomized clinical trials comparing Exosurf (synthetic, no apoproteins) to Survanta (beractant) and to Infasurf (calfactant) have been conducted.⁷⁻¹⁰ Results indicated that Exosurf patients did not respond as well (more persistent and severe respiratory

failure) and had a higher incidence of lung air leaks, but did not have a higher mortality, compared with the other surfactants studied. Respiratory distress syndrome mortality was so low, <5%, in both placebo controlled trials and in the comparison trials that many thousands would have to be enrolled to detect a RDS mortality difference if it exists.

Comparing Natural Surfactants

To date, large randomized clinical trials of Survanta and Infasurf have identified no differences in mortality between surfactants with apoproteins.^{11,12}

Conclusions From Large Clinical Trials

Surfactant therapy has never been able to diminish the incidence or severity of any of the other severe consequences of RDS or extreme prematurity, so no differences in mortality are likely to be identified

EVIDENCE FOR A MORTALITY BENEFIT FOR PORACTANT ALFA?

Poractant alfa/Pumactant Comparison Trial

In 2000, a randomized, comparison study of prophylactic use of lung surfactants in the UK between a pumactant (a synthetic surfactant used exclusively in the UK) and Curosurf (poractant alfa) was halted half way through because of a mortality difference.¹³ A difference in neonatal mortality was a secondary outcome. Did this study prove a mortality difference attributable to the different surfactants used?

The authors themselves identified that the 100 pumactant patients experienced a higher mortality than previously reported. “PredischARGE mortality...was greater than mortality in the pumactant group of the Ten Centre study (19.0%), and closer to the mortality in the control group of that study (29.7%).” On the other hand, poractant alfa patients had a lower overall mortality (14 of 99 [14%;

95% CI, 8% to 23%]) than the most recent large multicentered trials (442 of 2,168 [20%; 95% CI, 17% to 23%]).¹⁴ The authors did not comment on that difference. If one assumes the “respiratory deaths” in this study equal RDS deaths, the 5% mortality in the poractant alfa group is at the high end of expected, and the 9% non-RDS deaths is slightly, but not unduly, low. The respiratory death rate for the pumactant group is 21%, much higher than expected, and with no explanation provided. The non-respiratory death rate is 10%, which is very similar to the poractant alfa group. No significant difference was identified in the primary outcome (a measurement of the severity and persistence of RDS in survivors). Why would there be so great a difference in respiratory death without a difference in severity of RDS?

It is understandable why the study was stopped. Synthetic surfactants had been removed from the market in the United States because of lack of use. There was no reason to continue this trial. Yet it seems likely that unknown, uncontrollable, unpredictable factors generated a situation in which pumactant performed much more poorly than in previous studies and poractant alfa much better. Would that occur again? Replication is the primary standard of the scientific method and the reason regulatory agencies typically require efficacy to be demonstrated in 2 trials.

Poractant Alfa-Beractant Comparison Trials

The marketers of Curosurf (Chiesi Farmaceutici SpA in the European Union and Dey Laboratories, LP in the USA) have sponsored a series of small clinical trials that have compared the acute response of patients to prophylactic treatment at birth with poractant alfa or beractant.¹⁵⁻¹⁷ None of these prospectively identified any difference in mor-

tality. However, one of these, the trial lead by Ramanathan, purports to identify a survival advantage for the poractant alfa patients.¹⁷ The primary outcome—more rapid initial response for poractant alfa than beractant—replicated earlier studies and is expected for a surfactant with active levels of SP-B and SP-C compared to one with only SP-C activity. The study tested 2 doses of poractant alfa despite a previous study 5 times larger that had compared high and low doses.¹⁴ Differences in mortality were not part of the prospective study design, and were only revealed in post hoc analysis of the study data. Post hoc analyses are used to generate hypotheses, not test them. They should be interpreted with extreme caution and should be subjected to prospective, randomized trials.

In the 6 years since the completion of this clinical trial, neither the authors nor the sponsor has followed up with a prospective randomized, controlled clinical trial confirming this astounding finding.

Observational Study of US Hospital Data

At the Academic Pediatric Society meetings in 2007 in Toronto, a retrospective, epidemiologic paper was presented that reported that Curosurf patients experienced a lower all cause in-hospital mortality than beractant or calfactant patients.¹⁸ The study utilized a data base from 191 hospitals in a proprietary US hospital system and selected a cohort of patients with both an ICD-9 code for RDS plus treatment with a surfactant. The data included 24,907 patients from June 2003 through January 2006. Mortality rates were reported as 6.25% for poractant alfa, while those for beractant (8.15%) and calfactant (8.31 %) were one third higher.

Epidemiologic studies generate hypotheses, they do not evaluate them.

Yet this study was stated to derive from a prospective study (the 2004 study of Ramanathan et al), a reverse of legitimate scientific inquiry. First, the mortality rates for all the surfactants are much lower than in any large prospective trials of any surfactants for treatment of RDS suggesting many newborns in this database would have not qualified for a prospective trial. Second, the reliability of the ICD-9 coding is low. Why were not all surfactant-treated patients included in the study or all infants with RDS, regardless of treatments, to serve as a comparison group? Last, there is nothing in the composition, biophysical properties, or biologic activity of poractant alfa compared to beractant or calfactant that can explain a mortality benefit. If such a benefit were real it would have to derive from a property of a lung surfactant that has yet to be discovered.

EVIDENCE FOR A MORTALITY BENEFIT FOR LUCINACTANT?

Lucinactant Comparison Trial to Colfosceril palmitate and Beractant

In 2005, Moya et al published a large prospective randomized clinical trial that reported a higher RDS mortality rate for colfosceril palmitate (a synthetic surfactant) and beractant (a natural surfactant) than for lucinactant.¹⁹

Lucinactant is a synthetic surfactant not yet approved by the FDA containing 2 phospholipids and a synthetic peptide that the sponsor claims has an SP-B activity. Independent evaluation of the peptide concluded that it had an activity like SP-C rather than SP-B.²⁰ The mortality benefit claimed was in RDS related deaths. Lucinactant patients showed an RDS mortality (25 of 527, 4.7%) that was 4.7% and 5.8% lower than Exosurf (48 of 510, 9.4%, $P = 0.005$) and beractant (27 of 258, 10.5%, $P = 0.001$), respectively. While at first glance this trial appears rigorous, it has significant

limitations. First, this is an active-controlled study. To be valid, the reference drugs (the active controls, in this study colfosceril palmitate and beractant) must perform as well as they did in their placebo-controlled trials to assure that the active-controlled trial has “assay sensitivity”.²¹ In this trial, the colfosceril palmitate RDS-related death rate is 3-times higher than its 3% rate in placebo-controlled trials,²² and the beractant RDS-related death rate is 5 times the 1.9% its rate in its placebo-controlled trials.²³ Why were colfosceril palmitate and beractant so ineffective? Second, the RDS death rates for colfosceril palmitate and beractant in this study are close to the placebo RDS deaths rates of 11% and 16% in their trials, yet we know that all surfactants reduce RDS mortality compared to placebo. If colfosceril palmitate and beractant had performed as they did in their placebo-controlled trials, lucinactant would not have been able to show equivalence.

Although this trial included 50 hospitals, all are in countries in which high technology medicine like neonatal intensive care is not universal. Conducting complex randomized clinical trials was a new experience for these units. Study patients were infrequent with hospitals averaging <1 month. Also, recruitment descriptions cause concern: more than 90% of the 6,551 women at 24-32 weeks consented to the trial, but half were excluded by birth weight or lack of need to intubate at birth. Additionally, **more than half** of those consented AND eligible (~1600 patients) were **never randomized**.

There were 3 birth weight strata and 3 surfactant treatments giving 9 cells. One third of the patients were in 2 cells (lucinactant >1,000 g and colfosceril >1,000 g). The average numbers per hospital in the strata $\leq 1,000$ g birth weight were <6 patients in the lucinactant and

colfosceril palmitate groups and <3 patients in the beractant group. Because most RDS deaths occur in the <1,000 g birth weight strata, small volume center effects could have skewed the results. Small sites did have enough patients to enroll similar numbers of patients with birth weight <1,000 g in each surfactant treatment group in each strata. Thus any variability in mortality in tiny premature infants among the many centers was not adequately controlled.

Lucinactant's claim to a mortality benefit fails to meet the essential scientific standard for active-controlled trials as there is incontrovertible evidence that the active controls were effective. Additionally, the conduct of this trial in so many hospitals and in countries whose neonatal units have little experience in randomized clinical trials, as well as the small fraction of consented patients actually randomized, are issues that cause concern about the reality of the large mortality benefit for lucinactant that would not be predicted from previous basic science or clinical data.

MANUFACTURERS' RESPONSE TO PURPORTED MORTALITY BENEFIT

Poractant alfa

If the commercial promoters of poractant alfa considered possible the mortality benefit reported by Ainsworth et al 2000, or Ramanathan et al 2004, they would have supported a well-designed, actively controlled, randomized clinical trial to confirm this possibility. They have not. Another concern is the fact that one of the studies in which a mortality benefit was cited administered poractant in a prophylactic fashion, yet in the US poractant alfa is only approved for the treatment of RDS, not for its prevention. Thus, US neonatologists who wish to use poractant alfa prophylactically have to use it "off label" when there are already 2 lung surfac-

tants, beractant and calfactant, approved for prophylactic use.

Lucinactant

If the commercial promoter of lucinactant considered possible the mortality benefit reported by Moya et al 2005, they would have either initiated a well-designed, actively controlled, randomized clinical trial to confirm this possibility or requested a "Treatment Protocol" from the FDA to make this "life saving" medicine available on humanitarian grounds. They have done neither.

CONCLUSIONS

There is no valid clinical evidence for a mortality benefit of one surfactant preparation over another. This is consistent with what we know from more than 25 years of biochemical and biophysical studies. Recent comments in the literature purporting such benefit are derived from uncontrolled epidemiologic observations, or post hoc analyses of small clinical trials, and are not supported by several large, well-conducted, randomized prospective trials. The fact that preterm infant mortality is reduced by exogenous surfactants, but not by the type of exogenous preparation used, should not be surprising. While all exogenous surfactants reduce RDS and hence RDS-related complications, since the advent of surfactant replacement therapy in the 1980s mortality in these infants most often results from non-pulmonary conditions related to preterm birth (intraventricular hemorrhage, necrotizing enterocolitis, infection, etc.) and unrelated to surfactant-deficient, respiratory distress syndrome.

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