Observational study to compare the clinical efficacy of the natural surfactants Alveofact and Curosurf in the treatment of respiratory distress syndrome in premature infants

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Summary

Introduction: Natural surfactants have been shown to be superior to synthetic surfactants in the treatment of neonatal respiratory distress syndrome (RDS). In Germany, Alveofact® (A) and Curosurf® (C) are the most frequently used natural surfactant preparations. The aim of this retrospective, observational study was to compare the effects of A and C on gas exchange and outcome in premature infants.

Methods: During a 5-year period in our neonatal intensive care unit (NICU), 187 premature infants were treated with surfactant, with 82 receiving A and 105 receiving C. We recorded $F_{IO2}$ and gas exchange ($P_{aO2}/F_{IO2}$ ratio, $P_{aCO2}$, $S_{aO2}$) during the first 72 h after surfactant application and the incidence of outcome parameters at day 28 (bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (grade III or IV), patent ductus arteriosus (PDA), pneumothorax, necrotizing enterocolitides (NEC) and death). The differences between the patient groups were assessed by ANOVA or the calculation of relative risks. Bonferroni correction was used for multiple comparisons.

Results: There were no statistically significant differences between infants treated with A and C in mean gestational age (28.4 vs. 28.4 weeks), birth weight (1210 vs. 1258 g) and time of first surfactant application (60 vs. 90 min postnatal).
We observed no significant between group differences in course of $F_{IO2}$ and blood gases, or in incidence at day 28 of BPD (41.7% vs. 42.8%), IVH III/IV (18.3% vs. 14.3%), pneumothorax (9.8% vs. 4.8%), PDA (23.2% vs. 21.9%), PVL (7.3% vs. 9.5%) and death (17% vs. 17.1%). There were also no statistically significant differences in the subgroup of infants <28 weeks. The lower incidence of NEC in A compared with C (1.2% vs. 10.5%, $P = 0.01$) was not statistically significant after Bonferroni correction.

Conclusion: Independent of gestational age no significant difference in the clinical efficacy of A and C was observed.

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Introduction

Surfactant therapy reduces mortality\(^1\)\(^2\) and morbidity\(^3\) of preterm infants with respiratory distress syndrome (RDS). Various surfactant preparations are commercially available. Since large clinical trials showed that naturally derived surfactants had superior efficacy when compared with synthetic surfactant preparations,\(^4\) natural preparations are now used almost exclusively.

Various natural surfactants, derived from different animals, have been developed and tested.\(^1\)\(^3\)\(^–\)\(^6\) These commercially available preparations differ in their contents and composition, as well as in their in vitro\(^5\)\(^–\)\(^9\) and in vivo\(^6\)\(^,\)\(^10\)\(^,\)\(^11\) activity. A recent retrospective analysis by Clark et al.\(^2\) comparing the natural surfactants Infasurf\(^6\) and Survanta\(^6\) in a large series of neonates found no significant differences in mortality. In a prospective comparison by Baroutis et al.\(^3\) of three natural surfactants (Alveofact\(^6\) (A), Curosurf\(^6\) (C) and Survanta\(^6\) (S)) in infants with RDS, significant differences in clinical outcome with regard to C and S were observed. C was superior with regard to fewer days on mechanical ventilation ($P < 0.043$) and fewer days on supplemental oxygen ($P < 0.04$). Beyond that a reduced length of stay in hospital (LOS) of C compared to S ($P < 0.027$) and A ($P < 0.04$) was observed. Additionally, in another prospective comparison of C and S by Ramanathan et al.,\(^12\) a significantly reduced $F_{IO2}$ requirement was observed in C and a higher initial dose of C (200 mg) was associated with significantly reduced mortality ($P < 0.05$).

In Germany, bovine-derived Alveofact\(^6\) (A; Boehringer Ingelheim Pharma, Ingelheim, Germany) and porcine-derived Curosurf\(^6\) (C; Nycomed Pharma, Ismaning, Germany) are the most frequently used natural surfactant preparations, each of which has been independently tested in large clinical trials.\(^13\)\(^–\)\(^16\) Although these surfactant preparations contain surfactant-associated proteins B and C, their lipid compositions differ significantly. Furthermore, the total volume (in mL) to be applied on the basis of a comparable surfactant quantity (in mg) is significantly higher for C than for A. Plasmalogens and polyunsaturated fatty acid containing phospholipids (PUFA-PL), which improve the surface properties of lipid mixtures, are significantly higher in C than in A.\(^17\) A higher concentration of PUFA-PL and plasmalogen in tracheal aspirates of preterm infants immediately after birth has been associated with a lower incidence of bronchopulmonary dysplasia (BPD).\(^18\)

The differences between A and C in composition, dosage and viscosity are evident. We speculated that these differences may affect the clinical efficiency. Therefore, the aim of this study was to compare the immediate response to surfactant administration and long-term outcome parameters in infants treated with A and C.

Patients and methods

A prospective schedule for administration of exogenous surfactant was introduced into our neonatal intensive care unit (NICU) in 1995. Every infant requiring surfactant therapy, as judged by the attending neonatologist, received 100 mg/kg of A or C, with the surfactant changed quarterly. Surfactant was not blinded and administered by a rapid bolus injection into the distal endotracheal tube, while disconnected from conventional mechanical ventilation. After surfactant administration, no manual bagging was applied. Conventional ventilation was continued using the same adjustments of the ventilator as before surfactant administration.\(^19\)

We performed a retrospective analysis of data from all premature infants (gestational age <32 weeks) that received surfactant between 1996 and 2000. Infants included were those who showed signs of RDS\(^20\) and required mechanical ventilation with a $F_{IO2}$ higher than 0.3. Thirty-six infants with meconium aspiration syndrome or severe congenital anomalies, or those who received their first dose.
of surfactant at a postnatal age older than 3 h were excluded from analysis. To assess the effect of gestational age on clinical efficiency a subgroup analysis of infants <28 weeks was performed. Data obtained from patient charts included gestational age, birth weight, sex and multiple births, prenatal administration of steroids, mode of delivery, and APGAR scores at 1 and 5 min. To estimate the initial effect of surfactant therapy, we recorded \( F_{\text{IO}_2} \), \( P_{\text{aO}_2}/F_{\text{IO}_2} \), \( P_{\text{aCO}_2} \) and \( S_{\text{aO}_2} \) before and 1, 2, 6, 12, 24, 48 and 72 h after surfactant application. To determine clinical outcome, we obtained data from patient charts regarding the presence of BPD, defined as oxygen dependency at day 28\(^2\); necrotizing enterocolitis (NEC)\(^2\); hemodynamically significant patent ductus arteriosus (PDA)\(^2\); intraventricular hemorrhage (IVH) of grade III and higher\(^2\); periventricular leucomalacia (PVL)\(^2\); pulmonary bleeding; and air leaks or pulmonary intestinal emphysema.\(^2\)

The statistical significance of differences between A- and C-treated infants was tested by the \( \chi^2 \)-test or the Fisher’s Exact test for qualitative data and by ANOVA or Kruskal-Wallis test for quantitative variables as appropriated. The treatment effect on outcome parameters was assessed by the calculation of relative risks. Time-based analyses of days on ventilator and LOS, as well as age at the time the infant was weaned to room air were presented as Kaplan-Meier curves. Statistical analysis was performed using the software STATGRAPHICS Plus (Version 5, Manugistics Inc., Rockville, MD, USA). Statistical significance was defined as a \( P \)-value <0.05. Bonferroni correction was used for multiple comparisons.

**Results**

Of 223 infants receiving surfactant during the study period in our NICU, 36 had to be excluded from subsequent analysis because they fulfilled the exclusion criteria. Of the 187 infants whose charts were analyzed, 82 received A and 105 received C. Perinatal data of both treatment groups are shown in Table 1. After Bonferroni correction, there was no statistically significant difference in all data between the A- and C-treated infants.

**Immediate surfactant response**

When we analyzed data on surfactant administration, we observed no significant differences between the two groups of infants (Table 2). Neither application time nor the number of repeat administrations of surfactant differed significantly. The cumulative surfactant dosage was 208 ± 141 mg/kg in infants administered A and 183 ± 95 mg/kg in infants administered C (\( P < 0.05 \)).

Changes in \( F_{\text{IO}_2} \) and blood gases after surfactant instillation are shown in Fig. 1(a-d). In both groups, the \( P_{\text{aO}_2}/F_{\text{IO}_2} \) ratio and \( S_{\text{aO}_2} \) significantly increased after surfactant administration (\( P < 0.001 \)) and remained higher during the subsequent 72 h. The \( P_{\text{aCO}_2} \) significantly decreased after surfactant administration (\( P < 0.05 \)). When we compared the two groups, however, we observed no significant differences in any of the parameters shown (Fig. 1).

**Long term outcome parameters**

The outcome parameters are summarized in Fig. 2. Again, we did not detect any statistically significant differences between infants administered A and those administered C. The incidence of BPD was nearly identical in the two groups (41.5% for A and 42.8% for C). The only difference between the two treatment groups was the incidence of NEC (1.2% for A vs. 10.5% for C, \( P = 0.01 \)). After Bonferroni correction, however, this difference was not statistically significant.

### Table 1: Comparison of patient characteristics of the two treatment groups (shown are numbers with percentages in brackets or mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Alveofact(^\text{®} ) (N = 82)</th>
<th>Curosurf(^\text{®} ) (N = 105)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA (SSW)</td>
<td>28.4 ± 2.9</td>
<td>28.4 ± 3.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1210 ± 521</td>
<td>1258 ± 681</td>
<td>0.59</td>
</tr>
<tr>
<td>Male gender, N (%)</td>
<td>50 (60.9)</td>
<td>62 (59)</td>
<td>0.78</td>
</tr>
<tr>
<td>Twins or more, N (%)</td>
<td>19 (23.2)</td>
<td>24 (22.8)</td>
<td>0.22</td>
</tr>
<tr>
<td>No maternal steroids, N (%)</td>
<td>36 (43.9)</td>
<td>48 (45.7)</td>
<td>0.89</td>
</tr>
<tr>
<td>Caesarean section, N (%)</td>
<td>59 (71.9)</td>
<td>91 (86.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>APGAR 1 min ≤ 5, N (%)</td>
<td>55 (67.9)</td>
<td>73 (70.2)</td>
<td>0.79</td>
</tr>
<tr>
<td>APGAR 5 min ≤ 5, N (%)</td>
<td>13 (16)</td>
<td>19 (18.3)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Significance level after Bonferroni correction was \( P < 0.006 \). No statistically significant differences between the two treatment groups (A and C) were observed.
We also observed no statistically significant differences between A and C in the median duration of artificial ventilation (6.5 d (range, 2–24 d) vs. 6.0 d (range, 2–16 d)), duration of O₂ supplementation (20 d (range, 6–43 d) vs. 18 d (range, 5–44 d)) and the LOS (60 d (range, 26–89 d) vs. 59 d (range, 29–83 d)). Mortality was almost identical in the two groups (17.0% for A vs. 17.1% for C). To further demonstrate the effects of A and C on outcome Kaplan–Meier curves (Fig. 3a–c) were used showing the days on ventilatory support including CPAP (Fig. 3a), the days on supplemental oxygen (Fig. 3b) and the LOS in hospital (Fig. 3c). In neither of these curves a significant difference between A and C was detected.

A subgroup analysis in infants <28 and ≥28 weeks did not show statistically significant differences in all investigated parameters between A and C. To exemplify this result typical long-term outcome parameters are shown in Table 3.

### Table 2  
Time of first surfactant administration (median and range) and number of infants requiring more than one administration (number with percentages in brackets).

<table>
<thead>
<tr>
<th></th>
<th>Alveofact®</th>
<th>Curosurf®</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st application, min (range)</td>
<td>60 (20–150)</td>
<td>90 (30–180)</td>
<td>0.34</td>
</tr>
<tr>
<td>2 applications, N (%)</td>
<td>18 (21.9)</td>
<td>27 (25.7)</td>
<td>0.41</td>
</tr>
<tr>
<td>3 applications, N (%)</td>
<td>21 (25.6)</td>
<td>21 (20)</td>
<td>0.57</td>
</tr>
<tr>
<td>4 applications, N (%)</td>
<td>7 (8.5)</td>
<td>4 (3.8)</td>
<td>0.46</td>
</tr>
<tr>
<td>5 applications, N (%)</td>
<td>2 (2.4)</td>
<td>1 (0.9)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Significance level after Bonferroni correction was P<0.01. No statistically significant differences between the two treatment groups (A and C) were observed.

Figure 1 Values of FIO₂, PaO₂/FIO₂, PaCO₂ and SaO₂ (mean±SD) within the first 72 h after application of surfactant. Dotted line: C group; solid line, A group. No statistically significant differences in any of these parameters were observed.
Figure 2. Incidence of long-term outcome parameters (number and percentage in brackets) and relative risk with 95% CI. Significance level after Bonferroni correction was $P<0.006$. There were no statistically significant between group differences in any of the outcome parameters. Abbreviations: PVL, periventricular leucomalacia; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia.

Figure 3 (a–c) Kaplan–Meier curves showing the days on ventilatory support including CPAP (a), the days on supplemental oxygen (b) and the length of stay in hospital (c). Between Alveofact (black line) and Curosurf (gray line) there were no statistically significant between group differences in any of the outcome parameters.
Discussion

When we compared clinical data of preterm infants treated with either Alveofact® or Curosurf®, we found that these two surfactants did not differ with regard to the immediate response to surfactant administration (as determined by \(FIO_2\) and blood gases), the required dosage of surfactant, or the long-term outcome parameters. Thus, neither of these surfactant preparations seemed to be superior to the other. This, moreover, is clearly depicted in the Kaplan–Meier curves (Fig. 3a–c). Neither in days on ventilatory support and days and oxygen dependency nor the LOS any significant difference between A and C was found.

In this study we investigated infants <28 weeks of gestation with mean body weight of about 1200 g, which may include mild RDS patients with higher gestational age. Their inclusion could mask the difference between both surfactants A and C. However, a subgroup analysis in infants <28 and ≥28 weeks of gestation did not show any statistically significant differences in the short- and long-term parameters. Thirty-six infants of the enrolled patients fulfilled the exclusion criteria. An intention to treat analysis showed that the excluded patients did not affect the results of the study.

Although the incidence of NEC in infants treated with C was higher than in infants treated with A, the clinical importance of this difference is not clear, due to the small number of infants with NEC. Moreover, it was not statistically significant after Bonferroni correction. This difference may have been due to random causes, because clinical studies of Curosurf® have reported no increased risk for NEC.

Except for one study by Baroutis et al., there have been no direct comparisons of A and C, the two most frequently used surfactant preparations in Germany. The characteristics of our study cohort were similar to those observed in other studies of surfactants, and these characteristics did not differ between the groups of patients treated with A and C. The indication for surfactant application was identical for both treatment groups and was in agreement with previous studies and the recommendations of a German workshop. Premature infants (<32 weeks of gestation) with RDS, as judged by the attending neonatologist, received 100 mg/kg of either A or C if the \(FIO_2\) was higher than 0.3 to achieve \(SaO_2\) ≥88%. We used the same threshold of \(FIO_2\) as in other clinical studies of surfactant therapy, in that we excluded infants with meconium aspiration syndrome and severe congenital anomalies.

The present study included only those infants who received their first surfactant administration within 3 h of birth. Early administration is recommended and previous studies have performed it within 4 or 6 h of birth. Our median time of surfactant administration was distinctly shorter for both A (60 min; range, 20–150 min) and C (90 min; range, 30–180 min). The first surfactant administration in our study was comparable with those of previous studies at this time. These findings do not exclude that a clinically relevant difference may have existed. As recently shown 30 min difference may be clinically and physiologically important, enhancing for example the response to

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**Table 3**  Comparison of outcome parameters of both treatment groups (A and C) in infants <28 and ≥28 weeks of gestation.

<table>
<thead>
<tr>
<th></th>
<th>Alveofact®</th>
<th>Curosurf®</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age &lt;28 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>42</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>More than 1 surf. application (N)</td>
<td>27</td>
<td>28</td>
<td>0.72</td>
</tr>
<tr>
<td>BPD (N)</td>
<td>25</td>
<td>32</td>
<td>0.63</td>
</tr>
<tr>
<td>IVH (N)</td>
<td>12</td>
<td>11</td>
<td>0.71</td>
</tr>
<tr>
<td>Ventilator days, median (range)</td>
<td>12 (1–148)</td>
<td>17 (1–58)</td>
<td>0.61</td>
</tr>
<tr>
<td>Length of stay, median (range)</td>
<td>80 (1–258)</td>
<td>78 (1–136)</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Gestational age ≥28 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>40</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>More than 1 surf. application (N)</td>
<td>12</td>
<td>20</td>
<td>0.77</td>
</tr>
<tr>
<td>BPD (N)</td>
<td>9</td>
<td>13</td>
<td>0.46</td>
</tr>
<tr>
<td>IVH (N)</td>
<td>3</td>
<td>4</td>
<td>0.76</td>
</tr>
<tr>
<td>Ventilator days, median (range)</td>
<td>3 (1–44)</td>
<td>3 (1–175)</td>
<td>0.71</td>
</tr>
<tr>
<td>Length of stay, median (range)</td>
<td>47 (1–332)</td>
<td>56 (1–175)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

In both subgroups no statistically significant differences between A and C were found.
weaning from oxygen. This time frame of 30 min for surfactant application was not widely accepted practice at the time when the study was performed. Meanwhile clinical practice is evolving such that surfactant is being used when indicated within 30 min of age in preterm infants intubated for respiratory distress.

In accordance with standard practice in Germany, surfactant was injected into the distal endotracheal tube by a rapid bolus, while the patient was disconnected from conventional mechanical ventilation, and manual bagging was not applied thereafter. The negative effect of bagging on surfactant efficacy meanwhile provides support for this procedure. After surfactant administration, conventional ventilation was continued using the same ventilator settings as before to rapidly establish normal lung volume without vigorous ventilation.

We observed no statistically significant differences in cumulative dosage of A and C or in the number of repeat surfactant applications (Table 2). Interestingly, the recommended dosages for A, 50–100 mg/kg, differ from those for C, 100–200 mg/kg. In our study, the initial dosage ought to be 100 mg/kg irrespective of the surfactant used. This has been the clinical practice in our unit during the study period. We, however, acknowledge that recent studies have consistently shown that using 200 mg/kg initial dose of C resulted in faster weaning of FIO2 compared to Survanta and was even associated with decreased mortality. The total dosage of A, however, was 208 mg/kg, which is higher than the recommendations and actually related to the repetitive application. By contrast, the total dosage of C was 183 mg/kg, which is in the recommended range. Although not statistically significantly different between A and C it is not known, however, if a higher dosage of C would have affected the outcome of our study. Unlike the dosage, the instilled volume of both surfactants differed significantly (4.9 ± 3.4 mL in A vs. 2.7 ± 1.4 mL in C, P < 0.05) due to the differences in the dilution (A: 120 mg in 2.4 mL, C: 120 mg in 1.5 mL) supporting that type of surfactant used did not have any influence on clinical outcome.

We recently showed that C has higher concentrations of plasmalogens and PUFA-PL when compared with A. Plasmalogens and PUFA-PL improve the surface properties of lipid mixtures. Furthermore, high concentrations PUFA-PL and plasmalogen in the tracheal aspirates of preterm infants were associated with a lower incidence of BPD. Thus, we expected that C would have greater clinical benefit than A, due to the higher plasmalogen and PUFA-PL concentrations in the former. We found, however, that these two preparations had similar clinical benefits. There may be several reasons for this.

First, our study had some methodological limitations. Although the allocation to each group was prospectively randomized by quarterly changes in the use of these surfactant preparations, the intervention was not blinded. However, since a large number of patients were treated, there is less likelihood for bias in the analyzed parameters.

Second, the impact of the exogenous surfactant on the overall lipid composition of endogenous surfactant may be too small or too short lived to exhibit any clinical effects. We did not analyze lipid composition after surfactant administration; therefore, we do not know whether surfactant administration altered overall lipid composition.

Third, the lower viscosity of Curosurf should lead to better distribution of surfactant. However, we did not observe any differences in oxygenation following surfactant administration. Thus, the clinical relevance of low viscosity remains unclear.

In summary, despite the differences in composition and biophysical properties of the two surfactant preparations, A and C, we observed no statistically significant differences in gas exchange and outcome parameters in preterm infants treated with these two preparations. Thus, large clinical studies are further necessary to assess the clinical efficiency of new surfactants, in particular for the newer peptide containing synthetic surfactants.

### Acknowledgments

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### References


