Respiratory outcomes following 100 mg/kg v. 200 mg/kg of poractant alpha: A retrospective review

E Cloete,1,2 MB ChB, FRACP; CLo,1 MN (Neonatal); MJ Buksh,1,4 MBBS, FRACP

1 Auckland City Hospital Newborn Services, Auckland, New Zealand
2 School of Medicine, University of Auckland, New Zealand

Corresponding author: E Cloete (elzac@adhb.govt.nz)

Background. The treatment guideline for the management of respiratory distress syndrome in the newborn unit at Auckland City Hospital (ACH), Auckland, New Zealand, was amended in July 2010. In keeping with current evidence, the initial dose of poractant alpha was increased from 100 mg/kg to 200 mg/kg. The outcomes of newborns requiring treatment with surfactant before and after this change were reviewed.

Methods. Electronic clinical records were reviewed of infants admitted to ACH who received surfactant during the period December 2008 - December 2011. There were two groups: group A were infants who received 100 mg/kg of poractant alpha as an initial dose (December 2008 - June 2010), and group B were infants who received 200 mg/kg as an initial dose (July 2010 - December 2011). Infants with congenital anomalies and those treated with surfactant before transfer to ACH were excluded.

Results. A total of 256 infants were included in the analysis, 118 in group A and 138 in group B. Infants in group B had a higher median gestational age (28 v. 27 weeks; p=0.08) and birth weight (1 065 g v. 930 g; p=0.008) compared with infants in group A. Significantly more infants in group A received more than one dose of surfactant (33.9% v. 15.9%; odds ratio 2.7; p=0.0008). Infants in group B showed a significant reduction in oxygen requirement after the administration of surfactant (p=0.0003).

Conclusion. The administration of 200 mg/kg poractant alpha led to a significant improvement in oxygenation and a reduction in the need for further doses of surfactant.

S Afr J CH 2013;7(4):148-152. DOI:10.7196/SAJCH.634

Surfactant replacement therapy has revolutionised neonatal respiratory care over the past two decades. Whether given prophylactically or as rescue therapy to newborns with or at risk of developing respiratory distress syndrome, it reduces the incidence of air leaks and improves survival.1-3 It has also been shown to improve ventilation and oxygenation in the first 48 - 72 hours after birth.4 According to the European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants,5 at least 100 mg/kg of phospholipid is required for the management of neonatal respiratory distress syndrome. Recent pharmacokinetic and clinical data suggest that a dose of 200 mg/kg of phospholipid has a longer half-life and is associated with a better acute response and a reduced need for subsequent doses of surfactant therapy than lower doses.6-8

Poractant alpha (Curosurf), a natural porcine-derived surfactant, is the preparation used by the newborn services at Auckland City Hospital (ACH), Auckland, New Zealand. In our unit the following infants qualify for a dose of surfactant: (i) infants ≤30 weeks’ gestational age (GA) who require ventilation; and (ii) infants >30 weeks’ GA with clinical, radiological and laboratory findings suggestive of moderate to severe surfactant deficiency. The guideline for administering poractant alpha for the management of respiratory distress syndrome in neonates at ACH was amended in July 2010.9,10 Before this, infants were given an initial dose of 100 mg/kg. The dose remained 100 mg/kg when a second or third dose was administered. From July 2010, infants have been given 200 mg/kg as an initial dose and 100 mg/kg subsequently if further doses are required. The current guideline is in accordance with the recommendations from the manufacturer of poractant alpha2 as well as the consensus guideline.11 The unit’s criteria for administering a second dose of surfactant (the need for positive-pressure ventilation and/or an oxygen requirement >30%)12 have remained unchanged.

In this retrospective study, we compared the outcomes of a cohort of infants treated with an initial dose of 200 mg/kg poractant alpha after our amended guideline came into effect with a historical group of similar infants treated with 100 mg/kg.

Methods

This was a retrospective review of respiratory outcomes of neonates receiving treatment with surfactant over a 3-year period. Data were collected from ACH electronic medical records and the newborn services database. Infants admitted to the newborn unit at ACH who received at least one dose of poractant alpha during the period December 2008 - December 2011 were identified from the database and divided into two groups: group A were infants who received 100 mg/kg of poractant alpha as an initial dose (December 2008 - June 2010), and group B were infants who received 200 mg/kg as an initial dose (July 2010 - December 2011).

Infant records were reviewed by a neonatal fellow and a neonatal nurse specialist. The primary outcomes were: (i) duration of oxygen supplementation; including the need for and duration of home oxygen; (ii) the change in fraction of inspired oxygen (FiO2) following the first dose of surfactant (FiO2) immediately before and 1 hour after the administration of surfactant was recorded; oxygen delivery aimed to keep saturation levels within the target range13; (iii) the need for subsequent doses of surfactant and the time to administration; (iv) duration of mechanical ventilation; (v) rates of pneumothoraces; and (vi) death due to all causes. Secondary outcomes reviewed were: (i) major cerebral abnormality on head ultrasound (periventricular leukomalacia, hydrocephalus, grade 3 or 4 intraventricular haemorrhage); (ii) pulmonary haemorrhage (presence of fresh blood up endotracheal tube); (iii) necrotising enterocolitis (Bell stages IIA - IIIIB); (iv) retinopathy of prematurity (stage ≥3); (v) acquired pneumonia or sepsis (culture proven); (vi) patent ductus arteriosus (treated medically or surgically); and (vii) duration of hospital stay.
Data were analyzed using JMP V10.0 (SAS Inc.) statistical software. Results from the two groups were compared using Pearson’s chi-square test for categorical measures and Wilcoxon’s rank sum test or analysis of variance, as appropriate, for continuous measures. Odds ratio (OR) p-values were likelihood ratio based. Adjustments for confounders were undertaken using multivariable logistic regression.

Ethics approval was obtained from the Northern X Regional Ethics Committee, New Zealand.

Results

A total of 3,044 infants were admitted to the ACH newborn unit over the 36-month period 1 December 2008 - 31 December 2011. Of these infants, 570 (18.7%) had a GA of <32 weeks. A database search identified 277 infants (9.1% of total admissions) who received treatment with surfactant during this period, 128 in group A and 149 in group B. After excluding infants with congenital anomalies and those who were treated with surfactant before transfer to ACH, a total of 256 infants were included in the analysis, 118 in group A and 138 in group B. Patient characteristics are described in Table 1. Infants in group B had a higher median GA based on early antenatal scan findings (28 v. 27 weeks; p = 0.52) and birth weight (BW) (1,065 g v. 930 g; p = 0.08) than infants in group A; furthermore, 85.6% of infants in group A had a very low BW (<1,500 g) compared with 75.4% of infants in group B (Fig. 1). Gender distribution, the number of multiple births, births by caesarean section and the number of infants who received a complete course of antenatal steroids were similar in the two groups (Table 1).

Results for four primary outcomes are shown in Table 2. There were no statistically significant differences between the two groups for any of these outcomes. There was, however, a trend towards shorter duration of mechanical ventilation as well as lower rates of pneumothoraces and mortality in group B. Infants in group B showed a significantly greater reduction in oxygen requirement after the administration of surfactant (p = 0.0003).

Fifty-seven per cent of infants in group A and 29% in group B received the first dose of surfactant within 15 minutes of birth. Eighty-six infants, 44 in group A (37.3%) and 42 in group B (30.4%), received the first dose beyond 2 hours of age. The median time to the administration of the second dose was 10 hours in group A and 12 hours in group B.

We performed a subgroup analysis comparing the outcomes for very-low-birth-weight (VLBW) infants in the two groups (Table 3). There were 101 infants in group A and 104 in group B with a BW of <1,500 g. In this

| Birth weight (g) | Poractant alpha 100 mg (N=118) | Poractant alpha 200 mg (N=138) | p-value |
|-----------------|-------------------------------|-------------------------------|---------|
| <1,000 g        | 80                            | 100                           | 0.08    |
| 1,001 - 1,499 g | 70                            | 90                            | 0.08    |
| 1,500 - 2,499 g | 60                            | 80                            | 0.08    |
| ≥2,500 g        | 50                            | 70                            | 0.08    |

Table 1. Patient characteristics

| Characteristic                      | Poractant alpha 100 mg (N=118) | Poractant alpha 200 mg (N=138) | p-value |
|------------------------------------|--------------------------------|--------------------------------|---------|
| Male gender, n (%)                 | 60 (50.9)                      | 79 (57.3)                      | 0.30    |
| Birth weight (g), median (range)   | 930 (470 - 3,096)              | 1,065 (480 - 3,620)            | 0.08    |
| Gestational age (weeks), median (range) | 27 (23 - 36)                  | 28 (23 - 39)                  | 0.52    |
| Caesarean section, n (%)           | 78 (66.1)                      | 89 (64.5)                      | 0.78    |
| Multiple birth, n (%)              | 32 (27.1)                      | 33 (23.9)                      | 0.20    |
| Antenatal steroid course completed, n (%) | 65 (55.1)                    | 79 (57.3)                      | 0.79    |
cohort the percentage of infants who required respiratory support beyond 28 days of age was higher and the median duration of ventilation was longer compared with the cohort as a whole. Rates of pneumothoraces were significantly \( p = 0.05 \) lower in infants who received 200 mg/kg of surfactant than in those who received 100 mg/kg. There were no other significant differences between the two groups.

We also compared the outcomes for the infants in the two groups who were treated with a single dose of surfactant (Table 4). There were no statistically significant differences between these groups.

The mortality rate was significantly higher among infants who required more than one dose of surfactant, regardless of the size of the initial dose (27.5% of infants in group A and 22.7% of infants in group B who required more than one dose of surfactant died). Results of the secondary outcomes are shown in Table 5. Significantly fewer infants in group B received treatment for patent ductus arteriosus \( p = 0.008 \). There were no other significant differences between the groups. These complications are mostly associated with VLBW infants, so it made no material difference when infants with a BW >1 500 g were excluded from the analysis. The median (range) duration of hospital stay was 87 days (24 - 141 days) for VLBW infants in group A and 86 days (20 - 196 days) for group B \( p = 0.33 \).

**Discussion**

Safe and effective surfactant replacement therapy has been in use since the early 1990s. More recent studies have focused on establishing the optimal dose. Randomised controlled trials have shown that multiple doses of surfactant reduce rates of air leak syndromes and mortality among infants at risk of or with established respiratory distress syndrome. A wide range of dosing schedules as well as different types of surfactant have been used in these studies.

| Table 2. Primary outcomes | Poractant alpha 100 mg (N=118) | Poractant alpha 200 mg (N=138) | \( p \)-value |
|--------------------------|-------------------------------|-------------------------------|---------------|
| Oxygen supplementation    |                               |                               |               |
| Respiratory support on day 28, n (%) | 63 (53.4) | 83 (60.1) | 0.27 |
| Discharged on home \( O_2 \), n (%) | 22 (18.6) | 36 (26.1) | 0.15 |
| Duration of home \( O_2 \) (months), median (range) | 4 (2 - 21) | 4 (2 - 12) | 0.90 |
| Duration of ventilation (days), median (range) | 2.75 (0 - 60.8) | 1.46 (0 - 63.2) | 0.67 |
| Pneumothorax, n (%) | 7 (5.9) | 5 (3.6) | 0.38 |
| Death, n (%) | 17 (14.4) | 12 (8.7) | 0.15 |
| \( O_2 = \) oxygen. |

| Table 3. Primary outcomes of infants with a birth weight <1 500 g | Poractant alpha 100 mg (N=101) | Poractant alpha 200 mg (N=104) | \( p \)-value |
|--------------------------|-------------------------------|-------------------------------|---------------|
| Oxygen supplementation    |                               |                               |               |
| Respiratory support on day 28, n (%) | 62 (61.3) | 68 (65.4) | 0.21 |
| Discharged on home \( O_2 \), n (%) | 22 (21.8) | 33 (31.7) | 0.11 |
| Duration of home \( O_2 \) (months), median (range) | 4 (2 - 21) | 4 (2 - 12) | 0.42 |
| Duration of ventilation (days), median (range) | 2.96 (0 - 60.8) | 1.95 (0 - 63.2) | 0.48 |
| Pneumothorax, n (%) | 6 (5.9) | 1 (0.9) | 0.05 |
| Death, n (%) | 16 (15.8) | 11 (10.6) | 0.13 |
| \( O_2 = \) oxygen. |

| Table 4. Outcomes of infants receiving only one dose of surfactant | Poractant alpha single dose 100 mg (N=78) | Poractant alpha single dose 200 mg (N=116) | \( p \)-value |
|--------------------------|-------------------------------|-------------------------------|---------------|
| Oxygen supplementation    |                               |                               |               |
| Respiratory support on day 28, n (%) | 40 (51.3) | 63 (54.3) | 0.70 |
| Discharged on home \( O_2 \), n (%) | 13 (16.6) | 28 (24.1) | 0.21 |
| Duration of home \( O_2 \) (months), median (range) | 3 (2 - 18) | 4 (2 - 12) | 0.48 |
| Pneumothorax, n (%) | 3 (3.8) | 5 (4.3) | 0.87 |
| Duration of ventilation (days), median (range) | 1.16 (0 - 44) | 1.04 (0 - 63) | 0.70 |
| Death, n (%) | 6 (7.6) | 5 (4.3) | 0.95 |
| \( O_2 = \) oxygen. |
The results of a survey conducted across 173 neonatal units in Europe to determine current clinical practice relating to surfactant administration were published in 2011.[17] Poractant alpha was the most commonly used surfactant preparation and was used by 148 units (86%). The most frequently used initial dose was 100 mg/kg (58%), followed by 200 mg/kg (39%). Doses of 200 mg/kg were only administered when using poractant alpha. Forty-three per cent of infants in this survey received a second dose of surfactant. It is not stated what percentage of these infants received 200 mg/kg as a first dose. We have shown that infants who received 200 mg/kg of poractant alpha are less likely to require additional doses than infants who receive a smaller initial dose. Sixty-three (24.6%) of the 256 infants in our study received more than one dose of surfactant. Significantly fewer infants required a second dose after initial treatment with 200 mg/kg (15.9% v. 33.9% of infants who received 100 mg/kg; p=0.0008). Cogo et al.[7] investigated the kinetics of surfactant disaturated phosphatidylcholine and found a significantly longer half-life in the 200 mg/kg group (32±19 hours) compared with the 100 mg/kg group (15±15 hours). We found that the interval between the first and second doses of surfactant tends to be longer after the administration of 200 mg/kg. Infants in the 200 mg group who required a second dose received it at a median time of 12 hours compared with 10 hours for the 100 mg group.

We have shown a trend towards shorter ventilation times, shorter hospital stays and lower mortality among infants who received 200 mg/kg of surfactant as an initial dose compared with 100 mg/kg. Although none of these findings reached statistical significance, they have clinical significance. In some clinical settings it may mean having a ventilator or cot space available for another sick infant. We have also shown a clear reduction in rates of patent ductus arteriosus requiring treatment and in the incidence of pneumothoraces among VLBW infants treated with 200 mg/kg of surfactant.

This study has a number of limitations. Data were retrospectively collected from electronic records, and the accuracy thereof therefore depends on the quality of record keeping. We were, however, able to obtain relevant data on all outcomes of interest in this study. The study sample size was small, and the results should therefore be interpreted with caution.

### Conclusion

In this retrospective study, we found that there was a significant improvement in oxygenation and a marked reduction in the need for further doses of surfactant after the administration of 200 mg/kg of poractant alpha compared with 100 mg/kg. These findings are in keeping with current literature and support the current guideline for the management of newborn infants with respiratory distress syndrome at ACH.

### Acknowledgements

We thank the Children’s Research Centre at Starship Children's Hospital for statistical advice. EC received a fellowship sponsored by the Starship Foundation.

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### Table 5. Secondary outcomes

| Condition                  | Poractant alpha 100 mg (N=118) | Poractant alpha 200 mg (N=138) | p-value |
|----------------------------|---------------------------------|---------------------------------|---------|
| Major cerebral abnormality, n (%) | 14 (11.9)                      | 17 (12.3)                      | 0.91    |
| Pulmonary haemorrhage, n (%) | 7 (5.9)                         | 4 (2.9)                        | 0.23    |
| Necrotising enterocolitis, n (%) | 10 (8.5)                       | 14 (10.1)                      | 0.64    |
| PDA treated, n (%) | 37 (31.4)                      | 24 (17.4)                      | 0.008   |
| Pneumonia/sepsis, n (%) | 41 (34.8)                      | 54 (39.1)                      | 0.46    |
| ROP stage ≥3, n (%) | 5 (4.2)                         | 5 (3.6)                        | 0.80    |
| Duration of hospital stay (days), median (range) | 79 (10 - 141)                | 73.5 (3 - 196)                 | 0.77    |

PDA = patent ductus arteriosus; ROP = retinopathy of prematurity.
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