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Surfactant Bolus Instillation: Effects of Different Doses on Blood Pressure and Cerebral Blood Flow Velocities

Key Words
Preterm infant
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Abstract
Fifteen preterm infants suffering from respiratory distress syndrome were randomly allocated to receive either high-dose (200 mg/kg) or low-dose (100 mg/kg) surfactant treatment. Retreatments were done with the low dose. Blood pressure, blood gases and cerebral blood flow velocities were determined before and after 24 bolus instillations. With the high dose mean blood pressure and mean cerebral blood flow velocity dropped significantly. With the low dose only mean cerebral blood flow velocity decreased; the course was unrelated to blood pressure or PCO_2 fluctuations. The mechanisms leading to the observed circulatory changes after surfactant instillation remain unclear.

Introduction

Controlled studies of surfactant substitution have impressively shown a reduction in mortality [1] and an even more pronounced decrease in the incidence of pneumothoraces in preterm infants with respiratory distress syndrome (RDS) [1].

RDS, its treatment and its complications are closely related to the occurrence of intra- and periventricular hemorrhages (IVH). Surfactant treatment allows to ventilate babies at lower pressures [2], to avoid 'fighting the ventilator' [3] and to reduce the incidence of air leaks. Since all these factors contribute to the pathogenesis of cerebral hemorrhage [4, 5], surfactant treatment should be expected to lower the incidence of this cerebral complication of RDS, too. However, it has been disappointing to see that this expectation has not been fulfilled [1]. Some authors even reported an increased indicence of IVH after surfactant substitution [6, 7].

Recent studies of systemic and cerebral hemodynamics after surfactant bolus instillation showed increases as well as decreases in

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arterial blood pressure (BP) [8–10]. Van Bel et al. [11] found a fluctuating pattern of cerebral blood flow velocities (CBFVs).

We investigated the effects of two different doses of a natural surfactant preparation on BP and CBFVs in premature infants with RDS to find out whether a lower surfactant dose causes less circulatory disturbances.

Patients and Methods

Between August 1990 and December 1991, our department participated in a randomized controlled multicenter trial on surfactant substitution ('Curosurf 4') [20] with the aim to evaluate two different dose regimens for the porcine surfactant preparation Curosurf [12–14]. The study protocol was approved by the local Ethics Committee.

Infants were eligible for 'Curosurf 4' if RDS was diagnosed clinically and radiologically, if the arterial/alveolar oxygen tension ratio was 0.22 or less, if they were less than 72 h of age, and if written parental consent had been obtained.

Fifteen infants were monitored for their circulatory reactions to surfactant bolus instillations after they had been randomly allocated to receive either high-dose (200 mg/kg body weight initially plus up to 4 doses of 100 mg/kg each after intervals of 12 h) or low-dose (100 mg/kg body weight initially plus up to 2 doses of 100 mg/kg each after 12 and 24 h) Curosurf treatment. Each dose was divided into two parts and instilled as described previously [13], with the infant's head turned on either side during instillation but returned to the midline immediately thereafter to avoid jugular venous occlusion. In total, 24 instillations were evaluated.

In these infants, CBFVs were measured by Doppler sonography carried out by one of two investigators (M.R., H.S.). A pulsed-Doppler, two-dimensional ultrasound scanner (Sonoline SL 2, Siemens, Erlangen, Germany) with a 7.5-MHz Doppler probe was used to measure CBFVs. This was done in the right internal carotid artery immediately beneath the lateral edge of the sella turcica. Doppler frequencies were recorded when the sharpest characteristic visual and highest audible signals were obtained [15]. A tracing of at least six equal heart cycles was printed out. Peak systolic and end-diastolic CBFVs could be read after internal computing of the Doppler frequencies; mean CBFV was determined by calculating the area under the Doppler curve according to Jorch [16]. As most infants did not have arterial catheters, systolic, mean, and diastolic arterial BPs were measured oscillometrically (Dinamap, Criticon Inc., Fla., USA). All measurements were performed in the supine position.

Data on CBFVs, BP, transcutaneous oxygen and carbon dioxide tensions ($tcPO_2$ and $tcPCO_2$) were obtained before and 2, 5, 10, 15, 20, 30 and 60 min after surfactant instillation. $TcPO_2$ and $tcPCO_2$ were verified by arterial blood sampling.

The Mann-Whitney U test was applied to evaluate differences between variables of the two groups treated with different doses of surfactant. For all repeated measurements, a two-factor analysis of variance was carried out, the factors being time and dose. A $p < 0.05$ was considered statistically significant. All calculations were done with the SPSS-PC+ statistical package (SPSS Inc., Chicago, Ill., USA).

Results

Of the 15 infants studied, median birth weight was 1,060 g (range 670–1,770 g), and median gestational age 29 weeks (24–31). Nine of them were boys. Seven of them had grade 3 or 4 RDS as judged by chest X-ray. Median FiO_2 before the first surfactant substitution was 0.80 (0.50–1.0).

Eleven initial high-dose instillations were evaluated and compared to 13 low-dose instillations which were either given initially or as retreatments. The age at surfactant instillations was not significantly different for the high-dose group as compared to the low-dose group (9 h, 3–67, vs. 17 h, 3–37; $p = 0.32$). FiO_2 decreased significantly with both regimens, but the effect of the high dose was more pronounced (fig. 1a). Accordingly, in 7 of 11 infants who received a high dose, the additional oxygen requirement was reduced by 50% or more within 1 h whereas only 1 of 13 patients showed such a response after a low dose ($p < 0.05$). After surfactant instillation, $tcPCO_2$ increased transiently (fig. 1b) without a significant difference between high and low dose. Systolic and mean arterial blood pressure dropped significantly after instillation of a

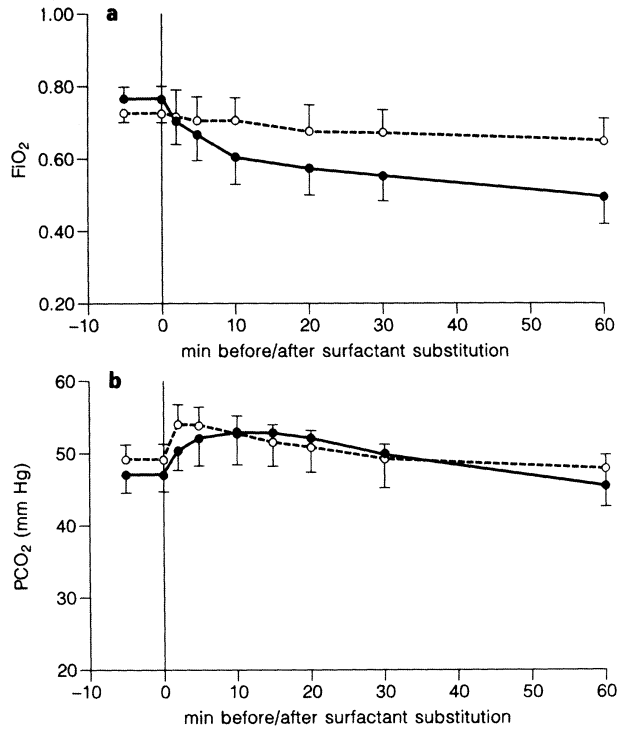

Fig. 1. Courses of FiO_2 (**a**) and PCO_2 (**b**) before and after different doses of surfactant. Mean ± SEM. ● = Instillation of 200 mg/kg (n = 11); ○ = instillation of 100 mg/kg (n = 13). The FiO_2 courses are significantly different ($p < 0.01$) by two-factor analysis of variance (dose, time). The courses of PCO_2 do not differ significnatly between the two doses; the increase after surfactant instillation is statistically significant ($p < 0.01$).

high dose. The lowest values occurred after 2 min; they recovered within 5 min. Following the lower dose of surfactant, BP showed no significant change (fig. 2). The mean CBFV in the right internal carotid artery decreased significantly after surfactant instillation with both dosing regimens (fig. 3a). Although the curves seem to be different, analysis of variance revealed that they go parallel with pretreatment values which are slightly but not significantly different ($p = 0.13$). End-diastolic CBFV decreased more dramatically: the values after surfactant instillation were significantly different from the pretreatment values between 5 and 30 min (fig. 3b). Again, the differences between the two groups depicted in figure 3 were not statistically relevant.

End-diastolic CBFV was zero or negative after 10 of 11 high-dose instillations and after 7 of 13 low-dose instillations (Fisher's exact test, $p = 0.12$).

The grade of improvement within 1 h after surfactant treatment (as judged by the decrease in oxygen requirement within this time, i.e. FiO_2 before surfactant substitution minus FiO_2 1 h thereafter) was not statistically related to the grade of the decrease in CBFVs (CBFV before surfactant substitution minus CBFV 2 or 5 min thereafter, respectively). This was true for mean CBFV as well as for end-diastolic CBFVs (data not shown).

Discussion

CBFVs in preterm infants are influenced by various factors such as birth weight, gestational age, postnatal age, persistent ductus

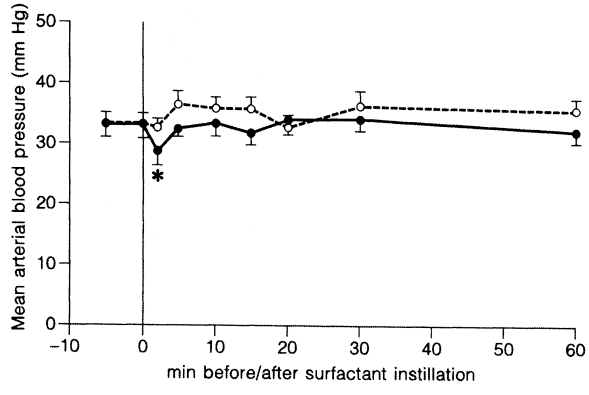

Fig. 2. Mean arterial blood pressure before and after different doses of surfactant. After the high dose (●, n = 11, mean ± SEM), the initial value after surfactant instillation was significantly different from the pretreatment values (* $p < 0.05$).

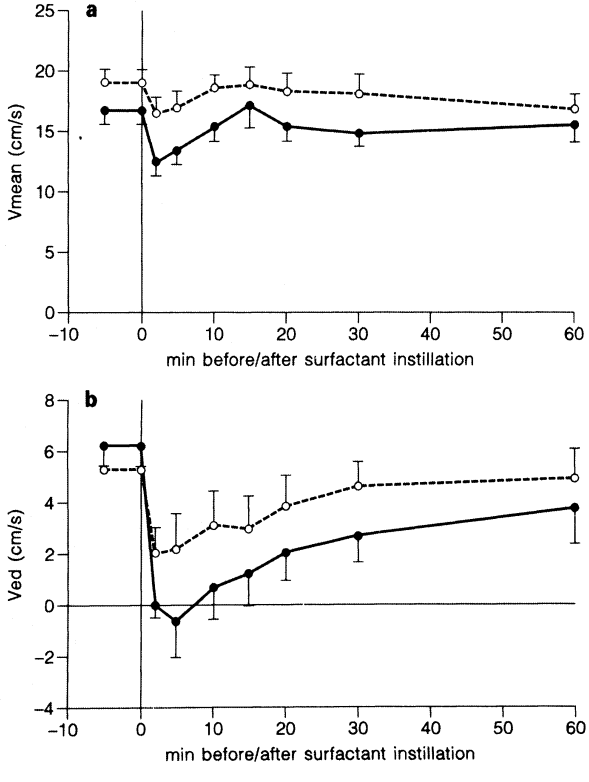

Fig. 3. Mean (**a**) and end-diastolic (**b**) CBFVs after different doses of surfactant. For both parameters, the pretreatment values were not significantly different between the two groups. After surfactant instillation, both mean and end-diastolic CBFVs dropped significantly in both groups as compared to the pretreatment values ($p < 0.01$), but were not different between the two groups ($p = 0.77$ for mean, $p = 0.72$ for end-diastolic CBFVs; two-factor analysis of variance).

arteriosus, intracranial abnormalities, and drug administration [17]. For the tracheal instillation of surfactant, transient changes in CBFVs have been described [9].

Similar to these investigators, we were interested in circulatory changes after surfactant instillation in very premature infants who represent the group of neonates with the most urgent need for surfactant treatment [3]. Our observations closely resemble those of Cowan et al. [9]: With the high Curosurf dose, a transient but significant decrease in arterial BP occurred. Similarly, the short-term elevation of $tcPCO_2$ is consistent with the observations made by Cowan et al. [9]. They also found a significant reduction in the mean CBFV in the middle cerebral artery after surfactant instillation, which lasted for about 20 min. In our patients, this decrease in the mean CBFV was shorter, yet a more sustained decrease could be observed for end-diastolic CBFV.

Although there was no significant fall in BP after the low surfactant dose in the present study, still a significant decrease in mean and end-diastolic CBFVs could be measured, which was not significantly different from the changes observed after high doses. (Only the recovery of the end-diastolic CBFV took more time after high-dose instillations.)

This observation is puzzling to us for the following reasons: We expected CBFV changes to go parallel with BP variations as in preterm infants cerebral perfusion is pressure-passive [5, 18]. We conclude that the alterations of CBFVs observed after surfactant bolus instillation do not depend on alterations of arterial BP.

We also anticipated that a more pronounced circulatory effect would occur with a rapid pulmonary response after surfactant treatment [19] when compared to a poor response. Most of the patients receiving a low dose revealed, in terms of oxygenation, such a poor short-term response. Nevertheless, changes in CBFV occurred in spite of a 'poor response' of oxygenation.

There is no easy explanation for these circulatory changes after surfactant treatment, neither for BP nor for CBFV alterations. The decrease in BP may be related to the rapid recruitment of atelectatic areas by surfactant treatment [21, 22], possibly leading to a decrease in the pulmonary vascular resistance and, consequently, to an increase in left-to-right shunting through the ductus arteriosus [11]. Also a decrease in peripheral vascular resistance as described by Skov et al. [10] and by Cowan et al. [9] may lead to a transient drop in BP. CBFVs may also be subject to variations in PCO_2. In the present study, however, the transient increase in PCO_2 after surfactant instillation should have caused an increase in CBFVs [17] but not a decrease as observed.

The alterations of CBFVs as observed by Cowan et al. [9] and in this study do not resemble the 'fluctuating pattern' of cerebral blood flow that has been described by van Bel et al. [11] and that has to be regarded as a high-risk factor for cerebral hemorrhages [15]. However, the results of Lohrer et al. [23] suggest that a drop in CBFVs after surfactant therapy is associated with an increased risk of cerebral hemorrhage.

Although each neonatologist tries to avoid abrupt changes in a preterm infant's condition and dislikes any interventions that cause sudden changes in BP or CBFVs, it should be emphasized that up to now there is no evidence that surfactant treatment actually causes cerebral bleedings. Nevertheless, it seems desirable to avoid abrupt CBFV changes, e.g. by modified instillation techniques. It is important to document that such modifications preserve the beneficial effects of surfactant substitution while avoiding circulatory disturbances.

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