Budesonide delivered by dosimetric jet nebulization to preterm very low birthweight infants at high risk for development of chronic lung disease

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We investigated the effect of an aerosolized corticosteroid (budesonide) on the oxygen requirement of infants at high risk for developing chronic lung disease (CLD) in a randomized, double-blind study. The study objective was to attain a 30% decrease in FiO_2 levels in the budesonide treatment group after 14 d of therapy. Thirty very low birthweight (VLBW) infants (median (range)) gestational age 26 wk (23–29) and birthweight 805 g (525–1227) were randomized. Inclusion criteria were mechanical ventilation on day 6 of life, or if extubated on nasal continuous positive airway pressure with $FiO_2 \geq 0.3$. The budesonide (Pulmicort™) dose was 500 μg bid, or placebo. The aerosol was delivered with a dosimetric jet nebulizer, with variable inspiratory time and breath sensitivity. Inhalations were started on day 7 of life. Twenty-seven patients completed the study. A significant lowering of the FiO_2 levels at 21 d of life was not detected. Infants who received budesonide were more often extubated during the study period (7/8 vs 2/9) and had a greater relative change from baseline in their oxygenation index (budesonide decreased 26% vs placebo increased 60%). Subsequent use of intravenous dexamethasone or inhaled budesonide in the treatment group was significantly less. All patients required O_2 supplementation on day 28 of life. At 36 wk postconceptual age, 61% of infants in the budesonide group needed supplemental O_2 as opposed to 79% in the placebo group. No side effects on growth or adrenal function were observed.

Conclusion: We conclude that inhaled budesonide aerosol via dosimetric jet nebulizer started on day 7 of life for infants at high risk for developing CLD decreases the need for mechanical ventilation similar to intravenous dexamethasone, but without significant side effects.

Key words: *Aerosol, budesonide, chronic lung disease, corticosteroid, preterm*

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In recent years the introduction of prenatal corticosteroid treatment to induce lung maturity in the fetus and surfactant administration to the infant with respiratory distress syndrome (RDS), combined with technical advances in neonatal intensive care, have resulted in an increase in the survival of VLBW infants (1). In these immature babies the incidence of chronic lung disease (CLD) is high (2, 3). CLD causes prolonged supplemental oxygen requirement, increases the length of stay in the neonatal intensive care unit and is the most common chronic lung disorder in infants (4).

Parenteral dexamethasone treatment of infants with CLD is widespread and the therapeutic rationale is that it can suppress the inflammatory process in the infant's lungs and modulate the repair process (5). The current literature supports the use of dexamethasone to facilitate extubation in infants with CLD, while the long-term benefits are more unclear. The timing of dexamethasone treatment, tapering of dose and length of treatment are still unresolved issues (6). Serious side effects associated with dexamethasone use are common (7).

Aerosolized corticosteroids are commonly used in childhood asthma and have shown minimal side effects compared to systemic corticosteroids (8–10). Studies examining the effect of aerosolized corticosteroids in neonates have shown beneficial effects on lung mechanics without reported side effects (11–15).

The aim of this study was to examine if an aerosolized corticosteroid, budesonide (Pulmicort™; Astra Draco, AB, Lund, Sweden) could decrease the oxygen requirement of infants at high risk of developing CLD.

Material and methods

Study design

The study was of a prospective, placebo-controlled, double-blinded design. The primary effect parameter was a 30% decrease in the value of the FiO_2 levels in the budesonide inhalation group after 14 d of therapy. To generate data on FiO_2 levels in infants with CLD we used historical data from 44 infants with CLD. Based on these data, a power analysis revealed that 15 patients in each arm of the study would be needed to achieve 80% power on a 5% significance level. Secondary effect parameters were rate of extubation, a/ApO_2 and oxygenation index (OI = mean airway pressure $\times$ FiO_2 $\times$ 100 / PaO_2).

The study was approved by the Karolinska Institute regional ethics committee and infants were enrolled after informed written consent was obtained from the parents.

Randomization

Randomization was computer-generated. Envelopes were numbered consecutively from 1 to 30. Clinical staff were blinded to the group assignment during the patient's hospital stay. The code was broken after the last patient was finished with inhalations. Patients who were not included in this study were offered corticosteroid treatment on clinical grounds by the attending neonatologist. This was the same at the end of the study period, when a decision was taken whether to start/continue aerosolized budesonide or give parenteral dexamethasone.

Inclusion criteria

The inclusion criteria were (i) mechanical ventilation on day 6 of life, or (ii) if extubated, nasal continuous positive airway pressure (NCPAP) with $FiO_2 \geq 0.3$. The exclusion criteria were congenital malformations, congenital heart disease and intraventricular haemorrhage (IVH) grades III–IV. Infants could be excluded during the study period by the decision of the attending neonatologist if they remained on mechanical ventilation with an increasing FiO_2 requirement greater than 0.6 and/or pCO_2 greater than 8.5 kPa (65 mmHg). Patients on high frequency oscillatory ventilation (HFOV) on day 7 of life could not be included, since inhalations could not be given through this device.

Patients

VLBW infants consecutively admitted to the NICU during the study period, from February 1996 to February 1998, were eligible for inclusion in the study. All clinical decisions on patient care were made by the attending neonatologists, who was blinded to the study medication.

RDS was diagnosed based on signs of respiratory distress, increasing oxygen requirement and characteristic radiographic findings. Two time limits for diagnosis of CLD were used (i) infants who required O_2 supplementation for more than 28 d had changes on chest radiography and respiratory symptoms (16), or (ii) a requirement for supplemental O_2 at 36 wk postconceptional age (17).

Infants diagnosed with RDS received natural bovine surfactant (Curosurf, Chiesi Pharmaceutici, Parma, Italy) 100 mg/kg/dose as rescue therapy when they needed mechanical ventilation. Infants were mechanically ventilated with Sechrist Infant ventilators (Sechrist Corporation, Anaheim, CA), Infant Star ventilators (Infrasonics, San Diego, CA) and the Sensor Medics 3100A high frequency oscillator (Sensor Medics Corp., LA) was used as rescue therapy when patients showed a poor response after two doses of surfactant. When FiO_2 levels were less than 0.3 and ventilator support minimal the infants were extubated to NCPAP (Infant Flow system, EME, UK). The patients were continued on NCPAP until they needed $FiO_2 < 0.25$ and had a stable breathing pattern, at which time they were switched to ambient O_2 for the remainder of oxygen therapy.

In our unit, i.v. dexamethasone can be used to facilitate extubation in infants who remain on mechanical ventilation at 2–3 wk of age. We start with a dose of 0.3 mg/kg/d for 3 d, which is then reduced to 0.15 mg/kg/d for the remainder of the first week. If the infant responds by successful extubation, the dose is tapered by 10% daily to a minumum of 0.05 mg/kg/d through day 14. For the third week this dose is given every other day and stopped after 3 wk of therapy. Infants diagnosed with CLD at 28 d of age can be started on inhaled budesonide 250 µg/dose/twice daily, which is continued until the patient is off supplemental oxygen.

Sepsis was diagnosed on the basis of a positive blood culture in combination with clinical signs, an abnormal white count and/or elevated C-reactive protein. Patent ductus arteriosus (PDA) was diagnosed based on clinical signs and confirmed with echocardiography. Intraventricular haemorrhage (IVH) was diagnosed with cranial ultrasound.

Inhalations

Budesonide (Pulmicort™) and a placebo vehicle without active corticosteroid was supplied in identical opaque, unmarked plastic vials by Astra-Draco Pharmaceuticals, AB, Lund, Sweden. Vials sufficient for each 14-d period/patient were kept in the hospital pharmacy in consecutively numbered cartons, numbered 1–30.

The inhalator used is an electronic dosimetric jet nebulizer (Spira Electro 4, Respiratory Center, Hämeenlinna, Finland). With this device one can select a variable inspiratory time (0.1–3 sec) and it delivers aerosol only through the whole of the inspiratory phase, but not during expiration. In spontaneously breathing patients, its action is controlled by a pressure-sensing device with variable sensitivity. The device can also be

manually triggered without the sensor in place. In patients on mechanical ventilation the inhalator was inserted in the inspiratory limb of the breathing circuit of the ventilator, between humidifier and tracheal tube. Manual triggering can then be done either in the expiratory or inspiratory phase during mechanical ventilation. During inhalation in spontaneously breathing infants, PEEP levels from 1 to 5 cm H_2O can be achieved by placing a ring valve between the nozzle of the inhalator and face mask. The face mask used in this study was a Laerdal mask (Laerdal, Norway) modified to fit onto the inhalator nozzle. The recommended nebulizing gas pressure is 2 bar and gas can be either room air or from a oxymixer via the pressure valve. In a recent study this device generated budesonide aerosol with a mass median diameter (MMD) of 3.6 μm (0.2 (range 2.7–4.1) and NaCl aerosol with a MMD of 3.6 μm (0.2 (range: 3.5–4.1) (18).

Before the start of the study the inhalator was tested during mechanical ventilation and in spontaneously breathing newborns. A micropore filter (supplied by Astra-Draco, Lund, Sweden) was placed between the tip of the tracheal tube and a test lung. Different lengths (5, 10 and 15 cm) of tubing from the nozzle of the inhalator to tracheal tube were tested. The inspiratory time of the inhalator was set at 0.3 sec and manual triggering of the device was initiated during the ventilator expiratory phase to load aerosol in the tubing before the start of inspiration (19). The ventilator was tested with a constant flow of 8 L/min, inspiratory time 0.4 sec, peak pressure 22 cm H_2O and PEEP of 4 cm H_2O. Two different volumes (1 and 2 mL) of budesonide suspension containing 0.25 mg of steroid were tested. The budesonide trapped in filter was then analysed using high-pressure liquid chromatography by Astra-Draco, AB, Lund, Sweden. The largest amount of budesonide extracted from filters during these trials was 10% of a 0.25 mg dose ($n = 5$; median 21.2 μg (16–40) when the distance of tubing from inhalator nozzle to tracheal tube was 10 cm, and the volume of liquid was 2 mL. The device was tested on 10 spontaneously breathing newborns, after permission was granted by the parents. A filter was placed between face mask and the inhalator nozzle. Approximately 14% of an 0.25 mg dose was extracted from these filters ($n = 10$; median 34 μg (21–51).

Based on results from the filter tests a nominal dose of 1000 μg/day was chosen, divided into two 500 μg inhalations, each with a volume of 2 mL. This would give an approximate deliverable dose of 100–140 μg. The volume nebulized during each inhalation was 2 mL. For patients on MV the inhalator inspiratory time was set at 0.3 sec and manual triggering was done during the expiratory phase. In patients on NCPAP the PEEP ring level and FiO_2 was set at the levels the patient was receiving. The infant's eyes were covered during inhalation and the mouth was rinsed out after inhalation, when possible. All inhalations were administered by the two principal investigators (BJ and ME). All infants who completed the study were successful in receiving their course of inhalations.

Investigations / data collection

Data on FiO_2 levels were collected daily. FiO_2 was recorded hourly and the values for each 24- h period were averaged to generate the FiO_2 level for each day. Mean airway pressure was recorded daily for infants on mechanical ventilation and CPAP pressure for infants on NCPAP. Arterial blood gases were obtained on days 7, 14 and 21. At those times, arterial / alveolar oxygen ratio (a/ApO_2) and oxygenation index (OI) were calculated. For patients on NCPAP, the daily CPAP pressure was used as an approximation of the mean airway pressure (20). We registered days on supplemental O_2, mechanical ventilation and NCPAP treatment, O_2 requirement at 28 d of age and at 36 wk postconceptual age.

Data on growth were collected as follows: daily weights, length and head circumference once weekly. Lower leg growth was measured once weekly with a knemometer (Force Institute, Copenhagen, Denmark) (21).

Adrenal cortisol response to stimulation was measured at the beginning and end of the study period (on the afternoon of days 7 and 21) with a low dose method. ACTH-(1-25) (Synacthen, Ciba-Geigy, Basel, Switzerland) 0.5 μg / 1.73 m^2 / dose was used. Baseline s-cortisol was measured at time 0 and the s-cortisol response 30 min later. A peak s-cortisol level of more than 500 nmol/L and an increment of the s-cortisol level above the basal one of at least 200 nmol/L was considered a normal response (22, 23).

Blood / urine glucose and blood pressure were recorded daily. Data were collected on culture proven sepsis, PDA, IVH and gastrointestinal problems.

Statistical analysis

For the analysis of continuous measurement data, a two-tailed Student's *t*-test was used. For clinical data, a non-parametric test (Mann-Whitney U) was used. For testing differences in frequencies the chi-squared test and Fisher's exact tests were used where appropriate. *P*-values of less than 5% were considered significant.

Results

Enrolled patients

Thirty infants who fulfilled the study inclusion criteria were enrolled in the study protocol. Their median (range) birthweight was 805 g (525–1227) and gestational age was 26 wk (23–29). Of patients eligible for study inclusion, one infant's parents declined to be included in the study protocol. Two eligible patients

Table 1. Perinatal and clinical characteristics of the study population. Values are shown as number (%) or median (range).

	Total ($n = 30$)	Budesonide ($n = 15$)	Placebo ($n = 15$)
Gestational age (wk)	26 (23–29)	25 (23–27)	26 (24–29)
Birthweight (g)	805 (525–1227)	766 (525–1122)	813 (630–1227)
Sex (male/female)	19/11	8/7	11/4
Delivery (vaginal/caesarean)	12/18	7/8	5/10
Prenatal steroids	22 (73%)	12 (80%)	10 (67%)
PROM	4 (13%)	4 (26%)	0
5-min Apgar score	7 (2–10)	7 (2–10)	8 (2–10)
RDS	29 (97%)	14 (93%)	15 (100%)
Surfactant treatment	29 (97%)	14 (93%)	15 (100%)
IVH any grade	9 (30%)	4 (27%)	5 (33%)
PDA at any time	18 (60%)	7 (47%)	11 (73%)
Sepsis at any time	21 (70%)	11 (73%)	10 (67%)

could not be included due to ongoing HFOV on day 7 of life. One patient in the budesonide group died on day 9 of life. This infant was diagnosed with sepsis (coagulase neg. staphylococcus) with a blood culture drawn on day 5 of life. The infant had DIC and IVH grade IV when therapy was discontinued. Two infants, one from each treatment arm of the study, were excluded by the attending clinician due to clinical deterioration while on mechanical ventilation. Both infants received i.v. dexamethasone according to the unit protocol (see page 1448). This left 13 infants in the budesonide arm of the study and 14 infants in the placebo group who completed the study protocol.

Perinatal data

The perinatal characteristics of the infants are given in Table 1. There were no significant differences in the gestational ages and birthweights between the budesonide and placebo groups. There were no significant differences in the 5-min Apgar score between the two groups of infants. Seventy-three percent of the mothers had received at least one dose of prenatal corticosteroid. The incidence of prolonged rupture of membranes was 15%.

Clinical data

The clinical characteristics are given in Table 1. Infants who received a diagnosis of RDS were 29/30 and all received surfactant rescue replacement therapy. There was no difference in the number of doses of surfactant given in the groups. The overall incidence of IVH grades I–II was 30% and the incidence of PDA diagnosed during the hospital stay was 60%. The incidence of culture proven sepsis during hospital stay was 75%. There were no significant differences between the groups in the incidence of IVH, PDA or sepsis. During the treatment period we recorded no cases of hyperglycaemia or elevated blood pressure over the 90th percentile. No cases of NEC or gastrointestinal bleeding were recorded. No new cases of IVH were recorded, except for the one case of IVH grade IV in the patient who died. Three cases of open PDA were diagnosed during the study period. Two in the budesonide group and one in the placebo group. Operative PDA closure was required for 4/11 (36%) infants and 2/7 (28%) infants in the placebo group and budesonide groups, respectively. There was a tendency for an increase in the diagnosis of sepsis in the budesonide group during treatment, compared with the placebo group, 8/13 vs 4/14 ($p = 0.08$).

Respiratory data

The respiratory characteristics can be seen in Tables 2 and 3. At study inclusion, 10 infants in each group were on mechanical ventilation and 5 infants in each group were on NCPAP with $FiO_2 \geq 0.3$. Excluded patients in the budesonide group (2) and placebo group (1) were on mechanical ventilation at study inclusion. During the study period, significantly more patients were extubated in the budesonide treatment group, 7/8 versus 2/9 ($p < 0.01$) (Table 2). We did not find a significant difference in FiO_2, OI or a/A pO_2 on days 7, 14 or 21

Table 2. Respiratory characteristics of infants who completed the study protocol. Values are shown as number (%) or median (range) (** denotes $p < 0.01$).

	Total ($n = 27$)	Budesonide ($n = 13$)	Placebo ($n = 14$)
Ventilator / NCPAP day 7	17/10	8/5	9/5
Ventilator / NCPAP day 21	8/19	1/12**	7/7
Ventilator time (d)	13 (1–40)	11 (1–40)	14 (1–38)
Time on NCPAP (d)	39 (15–80)	38 (26–79)	40 (15–80)
Suppl. O_2 time (d)	75 (42–183)	72 (42–150)	79 (54–183)
Suppl. O_2 at 28 d	27 (100%)	13 (100%)	14 (100%)
Suppl. O_2 at 36 wk	19 (70%)	8 (61%)	11 (79%)

Table 3. Oxygenation data of infants who completed the study protocol. Values are shown as mean (SD). * Denotes $p < 0.05$. For calculation of relative change, baseline was defined as 1 for each parameter with change as % from baseline.

	Total ($n = 27$)	Budesonide ($n = 13$)	Placebo ($n = 14$)
FiO_2 day 7	0.31 (0.05)	0.31 (0.03)	0.32 (0.06)
FiO_2 day 21	0.32 (0.08)	0.32 (0.07)	0.36 (0.07)
(Relative change)		1.02 (0.21)	1.10 (0.40)
a/ApO_2 day 7	0.37 (0.13)	0.33 (0.10)	0.40 (0.15)
a/ApO_2 day 21	0.35 (0.15)	0.34 (0.10)	0.35 (0.19)
(Relative change)		1.02 (0.24)	0.96 (0.67)
OI day 7	3.2 (1.3)	3.3 (1.3)	3.0 (1.3)
OI day 21	3.4 (3.0)	2.4 (1.2)	4.4 (4.0)
(Relative change)		0.74 (0.26)*	1.60 (1.30)

between the groups, although both FiO_2 and OI were lower in the budesonide group (Table 3).

All infants required supplemental oxygen at 28 d of age. In the placebo group, there were three patients who received i.v. dexamethasone after the study period was over and then continued on budesonide inhalations (according to unit protocol, page 1448). The remaining 11 patients received budesonide inhalations from 4 wk of age. In the budesonide group, one patient received i.v. dexamethasone after the study period. Seven patients were continued on budesonide inhalations and five patients did not receive any further steroid treatment ($p = 0.02$). At 36 wk postconceptual age, 8/13 (62%) patients in the budesonide group were still on supplemental oxygen, as opposed to 11/14 (79%) in the placebo group (n.s.). Calculation of number needed to treat (NNT) with budesonide for 2 wk, starting at 7 d of age was 7 (RR = 0.35, RRR 64.1%) to reduce parenteral dexamethasone treatment and 3 (RR = 0.61, RRR 38.4%) to reduce the need for any corticosteroid treatment (inhaled or parenteral).

For the 3 infants who were excluded to receive parenteral dexamethasone the number of days on mechanical ventilation were 28 (budesonide), 24 and 22 (placebo). All 3 infants remained oxygen-dependent past 28 d of age and at 36 wk postconceptual age.

Growth data

The growth parameters and serum cortisol values before and after stimulation are given in Tables 4 and 5. There were no significant differences in s-cortisol values before stimulation or in the response to ACTH-(1-25) stimulation in either group on days 7 and 21 (Table 5).

There were no differences between the groups in weights, length, head circumference or knee-heel length at the start of the study. The increase in weight, body length and lower leg length was the same in both groups. There was no difference in head growth between the two groups from birth until 21 d of age (Table 4).

Table 4. Growth parameters for the study patients. Delta (Δ) denotes the change in weight, body length and knee-heel length from day 7 to day 21 and for head circumference from birth until day 21. Values are shown as mean (SD).

	Total ($n = 27$)	Budesonide ($n = 13$)	Placebo ($n = 14$)
Δ weight (g)	112 (90)	107 (53)	104 (90)
Δ length (cm)	1.5 (0.9)	1.6 (0.8)	1.4 (0.9)
Δ knee-heel (mm)	2.9 (1.6)	2.7 (1.6)	3.0 (1.6)
Δ head circ (cm)	0.82 (0.7)	0.82 (0.7)	0.83 (0.2)

Discussion

In this study we found that infants started on budesonide aerosol inhalations on day 7 of life were extubated more frequently during the 2-wk study period compared with the placebo group. This is the same as is seen when i.v. dexamethasone is used to facilitate extubation in ventilator-dependent neonates (6). The early budesonide inhalations significantly decreased the need for further corticosteroid treatment after the study period. We assume that this reduction in corticosteroid use was real, since the decision on corticosteroid treatment was always made by the attending clinician, who was not aware of which treatment the infant had received during the study period. Recent studies evaluating the effect of aerosolized corticosteroids have also suggested a decrease in the need for parenteral corticosteroid use and/or increased extubation rate (14, 15, 24, 25).

The need for supplemental oxygen at 28 d of age was uniform in all patients in this study. However, at 36 wk postconceptual age, 61% of the infants in the treatment group needed supplemental oxygen versus 79% of the infants in the placebo group. This, combined with a significantly decreased oxygenation index and need for corticosteroid use after the study period in the budesonide group, may indicate a better pulmonary status in the infants who received early budesonide treatment.

FiO_2 levels in the budesonide-treated group were lower after treatment (0.32 vs 0.36), although they did not reach significance. One explanation for this finding could be that the sample size was based on calculations on patients with CLD treated between 1988 and 1990. That population does not fully represent the VLBW population in the late 1990s. Today, infants often do well initially, while complications, often in the form of

Table 5. Serum cortisol values and results of ACTH-(1–25) stimulation on days 7 and 21. All s-cortisol values are shown as nmol/L. Values are shown as mean (SD). Delta (Δ) denotes the increase from the baseline value on the given day.

	Total ($n = 27$)	Budesonide ($n = 13$)	Placebo ($n = 14$)
s-cortisol day 7	400 (160)	432 (180)	375 (143)
Δ s-cortisol day 7	261 (144)	234 (160)	282 (132)
s-cortisol day 21	386 (230)	405 (400)	370 (340)
Δ s-cortisol day 21	385 (239)	405 (294)	372 (198)

nosocomial infections and PDA, that are associated with modern neonatal intensive care contribute to the development of chronicity (26). This is evident in our patients, who had an incidence of PDA and sepsis of 60% and 75%, respectively, during their hospital stay. Therefore the absolute value of FiO_2 on any given day can be influenced by short-term fluctuations in clinical status, which decrease its value as a marker of pulmonary integrity.

Parenteral dexamethasone use is common in ventilator-dependent neonates and several investigators have confirmed the rapid improvement in pulmonary function leading to extubation (6). Systematic reviews on the use of early and moderately early postnatal systemic corticosteroids have found a decrease in the incidence of CLD at 28 d and at 36 wk corrected gestational age (27). However, systemic dexamethasone use is associated with serious side effects, such as hypertension, growth impairment and suppression of the hypothalamic-pituitary-adrenal (HPA) axis (7). Effects on the developing brain, leading to developmental delay, are perhaps the most serious recent concerns (28).

The rationale behind the use of aerosolized corticosteroids is that they would offer an increased pulmonary / systemic effect and therefore some sparing of side effects associated with parenteral corticosteroids. There is extensive experience with the use of aerosolized corticosteroid in young children in doses of 500–1000 μg/day of budesonide–doses that are relatively well tolerated with respect to side effects (8). However, a recent pilot study has reported moderately severe pituitary and adrenal suppression associated with the use of inhaled fluticasone proprionate in preterm infants (29).

There was no difference between the two treatment groups in adrenal response to low dose ACTH-(1–25). Baseline and stimulated cortisol levels were similar to previously reported levels in VLBW infants (30, 31). We found no adverse effects on growth in contrast to the growth retardation seen when systemic dexamethasone is used (32). Thus we feel it is safe to state that used in this way and for this length of time aerosolized budesonide is not associated with adverse effects on adrenal function or somatic growth.

Studies evaluating aerosolized corticosteroids in ventilated infants with evolving CLD have demonstrated short-term improvements in lung function (11–13, 15), increased extubation rate (15, 24), and less need for rescue parenteral steroids (14, 25). Compared to our study, the study by Cole et al. (25) shows similar results and has a similar randomized design, but used beclomethasone, a different dosing regime and way of administering aerosol. A recent systematic review of five randomized trials evaluating inhaled corticosteroids for preventing CLD did not demonstrate an effect in reducing the incidence of CLD, but supported a marginal effect in reducing the need for systemic corticosteroids (NNT = 10) (33). Our results would seem to add to the favourable effect of inhaled corticosteroid both by promoting extubation and decreasing the need for parenteral corticosteroid (NNT = 7).

Aerosol deposition is related to droplet size, which needs to be less than 5 μm diameter (respirable droplets) to deposit in small conducting airways and alveoli. Larger droplets mainly deposit in the oropharynx and upper airways. Budesonide has a mean particle diameter of 3.2 μm. The choice of nebulizer and inhalation technique will greatly influence drug delivery to neonates, which in turn will affect the desired effect. The wide range of doses, timing of therapy and different delivery methods may explain some of the variability and lack of effect in the above-cited studies. Most studies have delivered aerosol using metered dose inhalers (MDI) with spacers inserted into the ventilator circuit and hand-bagging is commonly involved. Variations of this technique have been found to deliver approximately 2–4% of the nominal beclomethasone dose to the lungs of tracheostomized rabbits (29). The MDI technique has the disadvantages of a risk of uneven dosage, interference with ventilation, increase in dead space and risk of volutrauma.

Jet nebulizers are suitable for use with drug suspensions such as budesonide. In filter tests, dosimetric jet nebulization has substantially increased the delivered dose compared with other inhalation techniques (30). Dosimetric jet nebulizers have a theoretic inspiration/expiration ratio of 100%. In practice, however, the ratio will never be this good, as some drug will always be exhaled. The disadvantages are that it is a relatively slow process, since the drug reservoir only empties during inspiration or when manually triggered. In this study we used a dosimetric jet nebulizer, which delivers budesonide in respirable particles (< 5 μm) with 10–14% of the nominal dose presented to the subject's airways. It was used on both intubated and spontanously breathing infants. All spontaneously breathing infants were able to trigger inhalation with ease due to the variable trigger pressure sensitivity and we experienced no adverse reactions during inhalation. A dosimetric system can offer advantages over other inhalation techniques in neonates, as demonstrated in this study. However, studies investigating further refinement of inhalation techniques and evaluation of long-term effects of inhaled corticosteroids are needed before this treatment modality can be uniformly recommended.

In summary, in a randomized, placebo-controlled, double-blinded study, we have found an increased rate of extubation during budesonide inhalation in VLBW infants. The use of corticosteroid in any form after the study period was also significantly less in the infants who received budesonide during the study period. No adverse effects were observed in the budesonide-treated infants. We conclude that early aerosolized budesonide is an alternative to facilitate extubation in VLBW infants, as opposed to parenteral dexamethasone.

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