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Effects of early dexamethasone therapy on pulmonary fibrogenic mediators and respiratory mechanics in preterm infants

Abstract

Corticosteroid administration may prevent chronic lung disease in premature newborns, perhaps by modulating the synthesis of various cytokines, including those involved in fibrogenic processes. This study analyses the levels of three fibrogenic cytokines, namely vascular endothelial growth factor, transforming growth factor-beta1 and basic fibroblast growth factor in tracheobronchial

aspirate fluids collected from 20 premature newborns randomly assigned to the early dexamethasone group or to the control group. Furthermore, pulmonary function tests were performed on days 0 and 2 following the start of therapy. The results show that early corticosteroid administration reduces transforming growth factor-beta1 and basic fibroblast growth factor levels, and abolishes the spontaneous vascular endothelial growth factor increase observed in untreated patients, concomitantly with significant improvement of dynamic lung compliance and shorter duration of the intubation period in the treated group of patients. Significant correlations were observed between the levels of transforming growth factor-beta1 and vascular endothelial growth factor, indicating that the production of both these cytokines is coordinated. Finally, transforming growth factor-beta1 ratios (day 2/day 0), representing early variations of the cytokine levels, were significantly different between treated and untreated subjects and correlated with the dynamic lung compliance ratios and the extubation day, suggesting that the downmodulation of some fibrogenic mediators may be involved in the mode of action of dexamethasone.

Full text

INTRODUCTION

Increasing evidence has accumulated in recent years suggesting that inflammation plays an important role in the pathogenesis of chronic lung disease of prematurity (CLD) [1].

The cytokine network is essential for orchestrating the host response to injury, which under normal conditions results in healing and resolution. The development of pulmonary fibrosis, a prominent feature of CLD [2-4], has been postulated to be a consequence of exaggerated repair processes.

The most potent collagen stimulator is transforming growth factor-beta1 (TGF-beta1), which also stimulates other extracellular matrix components [5]. This cytokine enhances collagen formation by increasing both the rate of transcription and the stability of the resulting transcripts [6]. TGF-beta1 simultaneously blocks matrix degradation by decreasing the synthesis of proteases and increasing the level of protease inhibitors. Vascular endothelial growth factor (VEGF) is a potent angiogenic and vascular permeability factor which is strongly up-regulated by hypoxia in a number of systems, including the

lung, where it may help mediate lung vascular permeability [7]. Basic fibroblast growth factor (bFGF) is widely expressed both by embryonic tissues, in which it has both mitogenic and morphogenic actions, and by human fetal tissues early in the second trimester and in human placenta up until term [8]. All these mediators are therefore known to be powerful fibrogenic agents while other cytokines, such as IFN-gamma, are capable of inhibiting collagen production.

Because of their strong anti-inflammatory properties, corticosteroids have been used to ameliorate or to prevent CLD. They also affect normal development, including the expression of growth factors such as VEGF, TGF-beta1 and bFGF. Corticosteroids, in fact, down-regulate VEGF mRNA induction in several cell types *in vitro* [9] and inhibit collagen synthesis *in vitro*, but the mechanism of this inhibition has been a matter of debate; one possible explanation is that corticosteroids act by inhibiting fibrogenic cytokines [10-13].

The reduction in lung inflammation, edema and fibrosis induced by the steroids is the most likely mechanism by which they produce a rapid improvement in lung function, with faster weaning from mechanical ventilation [14, 15]. Samples of tracheobronchial aspirate fluid (TAF) were collected and pulmonary mechanics were evaluated during a randomised, controlled trial, testing the ability of dexamethasone (Dex) to affect fibrogenic cytokine concentrations in the lung, and pulmonary mechanics in preterm infants. We hypothesized that early postnatal administration of Dex would both decrease the amount of VEGF, TGF-beta1 and bFGF in the pulmonary epithelial lining fluid (ELF), thereby reducing subsequent fibrotic processes and improving pulmonary mechanics.

METHODS

This clinical trial was carried out in our Neonatal Intensive Care Unit over a 1-year period ending in July 2000 and which included 20 neonates with birth weight ¾ 1,250 g and gestational age ¾ 32 weeks, who were oxygen and ventilator dependent on the 4th day of life and at high risk of CLD according to our scoring system [16]. Baseline characteristics of the preterm infants included in the study are shown in Table 1. No significant differences were observed between the two groups studied. After informed written consent from the parents, eligible infants were randomly assigned to the control group (Ctr-group) or to the treatment group (Dex-group). The infants in the Dex-group received Dex intravenously for 7 days according to the following schedule: 0.5 mg/kg/day for

the first 3 days of treatment, 0.25 mg/kg/day for the next 3 days and 0.125 mg/kg/day for the seventh day of treatment. The Ctr-group received no steroid treatment.

Tracheal aspirates and pulmonary function tests were performed 2-4 hours before the beginning of the study (on the 4th day of life), and 48 hours after. Infants with prenatal infections or pneumonia, congenital malformations and evidence of sepsis or pneumonia were excluded from the study at randomisation.

All infants were ventilated with time-cycled, pressure-limited ventilators and extubated to continuous positive airway pressure (CPAP) by nasal prongs. A single dose of 200 mg/kg of a pig-derived, natural surfactant (Curosurf, Chiesi) was given to each infant with hyaline membrane disease within the first six hours of life. Nine patients out of 10, in both groups, received natural surfactant, which is a current pharmacological treatment.

The aim of respiratory management was to maintain blood gas values with pH 7.30-7.45, Pa CO_2 45-55 mmHg and Pa O_2 50-70 mmHg. The weaning protocol started when the following ventilator setting was reached: peak inspiratory pressure (PIP) of 18 cm H_2O, positive end expiratory pressure (PEEP) ¾ 4 cmH_2O, respiratory rate (RR) of 20 breaths per minute, inspiratory time ¾ 0.5 sec, fraction of inspired oxygen ¾ 0.40. For all infants, the protocol for extubation was followed when they had been clinically stable for at least 6 hours. Subsequently, PIP and PEEP were held constant, while the RR was reduced by extending the expiratory time only, in steps of two breaths per minute, every 2 hours until an RR of 6 breaths per minute was reached. Before extubation all infants were switched to CPAP of 4 cm H_2O, delivered *via* the endotracheal tube for 2 hours.

A standardized procedure of tracheobronchial aspiration [17] was performed. Briefly, 1 ml x kg^{-1} of 0.9% sodium chloride was instilled into the endotracheal tube and after two or three ventilator cycles, the suction catheter was gently inserted 0.5 cm beyond the tip of the tube and the airway fluid was aspirated into a sterile specimen trap (Vigon, Ecouen, France), with 50 mmHg of negative pressure. This procedure was repeated a second time and, to rinse the suction catheter, normal saline was added up to a final volume of 2 ml. After collection,

TAF specimens were centrifuged at 1,000 G for 3 min; cell-free supernatants were immediately removed and frozen at - 70° C for later assay.

VEGF, TGF-beta1 and bFGF concentrations in ELF were determined using commercially available ELISA kits (R&D Systems Europe Ltd. 4-10, The Quadrant, Barton Lane, Abingdon, Oxon, UK), following the manufacturer's instructions. The TAF concentration of the three cytokines was recalculated as ELF concentration, using a dilution factor obtained by means of the urea method [18]. This method assumes that rapidly diffusing urea is present in equal concentrations in ELF and serum. Urea was measured following a previously described methodology [18, 19]. As reported in previous publications [19] and also confirmed in this study, the urea correction was important in evaluating the results.

In this study, in order to analyse the early effect of Dex treatment, the cytokine ratios for the values observed at times 2 and 0 (ratio t2/t0) were also calculated to underline the variation in levels rather than the absolute concentrations.

Pulmonary mechanics were measured during mechanical ventilation, as described by Bhutani *et al.* [20]. The babies were placed supine, whilst asleep, with their head in a neutral position. The ventilator rate was set to 60 breaths per minute, while PEEP was reduced to 2 cm H_2O so avoiding gas trapping, to overcome the spontaneous breaths of the babies and to completely adapt them to the mechanical ventilator. PIP was similar to that used for clinical ventilatory support. All the babies were ventilated with a 2.5 mm ID (internal diameter) endotracheal tube during the study period.

No sedation, muscle relaxants or esophageal balloon were used. Airflow, airways pressure and tidal volume were measured with the same equipment used by Hummler *et al.* [21]. Only mechanical breaths were analysed; esophageal pressure was not used in these small children because the contribution of the chest wall to overall total compliance is small in premature babies, although it could generate artefacts due to the incorrect positioning of the catheter and to the unreliable contribution of chest wall distortion [22].

Dynamic lung compliance (Cdyn), total lung resistance (Rt) and expiratory lung resistance (Re) were calculated by a computer program using the equation of motion, and linear regression analysis [23, 24]. Breaths fulfilling the following

criteria were analysed: a) inspiratory and expiratory volumes within 10% of each other, thus ruling out airleaks around the endotracheal tube; b) the correlation coefficient (r) for the calculation of compliance and resistance from the recordings of flow, volume and pressure >= 0.95.

Mean values from a minimum of ten complete, non-distorted mechanical breaths were taken as representative of the infant's pulmonary mechanics. At the 28th day of life, bronchopulmonary dysplasia (BPD) was defined according to Bancalari [25] as oxygen supplementation, respiratory distress and an abnormal chest radiograph.The BPD severity was assessed using previously described radiological BPD patterns [26]: BPD type 1 ("mild") consisted of bilateral, ill-defined pulmonary opacities that were predominantly perihilar and homogeneous. It is associated with a better prognosis and a very low mortality, in contrast to type 2 ("severe"), which consisted of a coarse reticulation characterized by streaky densities interspersed with small cystic translucencies. Type 2 BPD has a higher mortality from respiratory causes and is associated with more intensive support from artificial ventilation [27].

The study protocol and consent forms were approved by the Ethical Committee of the Department of Pediatrics.

Statistical evaluation

Due to the lack of previous, available data, the number of subjects analysed was as 10 per group in order to assess a pilot set of determinations.

The limited number of subjects examined and the variable ratios used in this study necessitated the use of non-parametric tests for the statistical comparisons, as specified in the text. Consequently, the correlations were analysed using the Spearman rank correlation test. Fisher's exact test was used for comparison of categorical variables. A p value < 0.05 was considered statistically significant.

Multiple regression analysis was conducted in order to evaluate the independence of gestational age, birth weight or treatment on cytokine concentrations or their ratios (Intercooled Stata 6 for Windows, Stata Corporation).

RESULTS

Three subjects in the Ctr-group (30%) were affected by severe BPD but none in the Dex-group. Moreover, treated infants were extubated significantly ($p < 0.05$) earlier than the untreated ones [median values (and range) of postnatal extubation day: 8 (6-13) and 17 (6-32)], respectively.

Figure 1 reports all individual points and changes for the three cytokines from day 0 to day 2 of treatment. ELF VEGF concentrations significantly ($p < 0.05$) increased in control, premature neonates two days after the beginning of the study, while they remained stable in Dex-treated neonates. In addition, the difference between the ratios t2/t0 was statistically significant ($p < 0.006$) when compared between treated and untreated babies.

ELF TGF-beta1 levels showed a different profile: in fact, they increased over time in untreated subjects ($p < 0.05$) (similarly to the ELF VEGF concentrations), but a significant fall ($p < 0.05$) in the ELF amounts was observed in Dex-treated newborns. A statistically significant difference between treated and untreated babies was found for both the absolute values at time 2 ($p < 0.01$), and the t2/t0 ratios ($p < 0.006$).

No significant changes were observed in ELF bFGF concentrations in untreated patients, but a significant difference ($p < 0.05$) was found for the levels in Dex-treated patients, suggesting that corticosteroids also modify the amounts of this mediator.

The similarities observed between the behaviour of VEGF and TGF-beta1 were also confirmed by the significant correlation found between their concentrations ($r = 0.51$, $p = 0.001$, $N-1 = 39$) or concentration ratios ($r = 0.65$, $p = 0.002$, $N-1 = 19$, Figure 2a). Furthermore, significant correlations were also observed between the VEGF or TGF-beta1 (Figure 2b) concentration ratios *versus* gestational age ($N - 1 = 19$, $r = - 0.50$ and $r = - 0.57$, $p = 0.03$ and $p = 0.01$, respectively) or birth weight ($N - 1 = 19$, $r = 0.49$ and $p = 0.03$ for both plots). No sex-related differences were observed (data not shown). A multiple regression analysis was also performed including cytokine levels, gestational age, birth weight and treatment (yes, no). TGF-beta1 variations between time 0 and time 2 were still statistically significant ($p < 0.05$), independently of gestational age and birth weight.

Regarding pulmonary mechanics, only Dex-treated infants showed significantly higher Cdyn median values ($p < 0.005$) when compared with the pre-treatment values: 0.87 ml/cm H_2O/kg (0.70-1.30) *versus* 0.50 ml/cm H_2O/kg (0.30-0.70). Furthermore, a significant difference was observed between treated and untreated patients at day 2 [median value: 0.87 ml/cm H_2O/kg (0.70-1.30) *versus* 0.50 ml/cm H_2O/kg (0.45-0.86), $p < 0.01$]. No significant changes were observed in the two groups as far as Rt or Re values were concerned (data not shown).

Some statistically significant correlations were observed between the cytokine levels and the clinical features or functional respiratory parameters. In fact, TGF-beta1 ratios correlated significantly with the extubation day ($N - 1 = 19$, $r = 0.65$, $p < 0.002$, Figure 2c) and with the Cdyn ratio values ($N - 1 = 19$, $r = - 0.55$, $p < 0.01$, Figure 2d). Moreover, a significant correlation was found between all Cdyn absolute values (at times 0 and 2) and corresponding values of TGF-beta1 ($N - 1 = 39$, $r = - 0.32$ and $p < 0.05$) or when only time 2 was examined ($N - 1 = 19$, $r = - 0.43$ and $p = 0.05$). No correlations were registered between cytokine levels (or their ratios) and the total lung resistance or expiratory lung resistance (data not shown).

As already mentioned, three untreated subjects were affected by severe BPD. Their TGF-beta1 values, recorded on day 2, were significantly higher ($p < 0.05$) than those of the newborns with mild BPD ($N = 11$) or without BPD ($N = 6$) (median concentration = 8.18 ng/ml, range 5.12-9.72 ; median concentration = 2.80 ng/ml, range 0.40-9.48 and median concentration = 1.68 ng/ml, range 1.40-1.96 respectively). For the same groups, no significant differences were observed on day 0 (data not shown). No significant variations were registered for VEGF and bFGF concerning BPD, both on day 0 and day 2, even if the data were in keeping with increased values of these mediators in severe BPD (data not shown).

On day 2 of the study, the three patients with severe BPD showed significantly higher values of Rt ($p < 0.05$) (median = 170 cm H_2O/l/sec, range 149-201; median = 125 cm H_2O/l/sec, range 75-158 and median = 108 cm H_2O/l/sec, range 89-128 respectively) as compared with the other babies with mild BPD or without BPD, and significantly higher values of Re ($p < 0.05$) (median, 271 cm H_2O/l/sec; range, 254-276; median, 162 cm H_2O/l/sec; range, 111-248; median, 142 cm H_2O/l/sec; range, 97-187 respectively). Finally, Cdyn values in severe BPD infants were lower (median = 0.50 ml/cm H_2O/kg, range 0.45-0.73), as compared

to patients with mild BPD (median = 0.73 ml/cm H_2O/kg, range 0.45-1.2) or without BPD (median= 1.07 ml/cm H_2O/kg, range 0.85-1.3) ($p < 0.05$).

DISCUSSION

Corticosteroids have been reported to protect premature newborns from CLD [28, 29], even if the best time to give it, and the minimum efficacious dose are still to be defined.

On the other hand, there are many short-term side effects associated with Dex therapy, including increased incidence of sepsis, hyperglycemia, hypertension, myocardial hypertrophy, gastrointestinal bleeding and poor growth [28, 30-33]. Lastly, there is concern that post-natal steroids could increase the risk of long term neurological damage [34, 35]. All these considerations are of great importance in deciding whether or not Dex should be administered, even if the available data support the idea that they are important for pulmonary outcome. Consequently, elucidating the possible mechanisms of action of steroid therapy, while preserving the beneficial effects and reducing both the duration of treatment and short and long-term side effects, seems to represent an important goal.

The study of pulmonary mechanics in association with the determination of the concentrations of some cytokines, recently suggested as having an important role in the development of CLD and in the fibrotic response of the premature lung [2, 10, 36-38], could be useful in studying the short-term effects of dexamethasone on lung inflammation. In fact, Dex mechanisms of action are possibly mediated by blocking the release of different pro-inflammatory biological modifiers and reducing the fibrotic processes driven by the so-called fibrogenic cytokines (both pro-inflammatory and pro-fibrotic mediators are strictly interrelated). Our report concomitantly analyses ELF TGF-beta1, VEGF and b-FGF levels before and 48 hours after early steroid therapy started on the 4th day of life. In fact, Dex generally shows rapid, clinical anti-inflammatory effects and often determines a rapid extubation in responding patients (limiting the observation period of TAF collection). A group of control subjects not receiving this early therapy was employed for comparison.

The steroid therapy significantly reduced (mantained in the case of VEGF), in a two day period, the ELF concentrations of the three cytokines tested in terms of absolute values and/or in terms of post-/pre-therapy ratios. To confirm a possible common regulation of the ELF level variations of the different cytokines, a correlation analysis was performed.

The levels of TGF-beta1 and VEGF, often produced by the same cells [39, 40], were significantly correlated, in keeping with the knowledge that VEGF is induced by TGF-beta1 in different cell systems [13, 41], as previously observed in other models [42, 43]. Furthermore, the levels of these two cytokines behaved similarly when the corresponding day 2/day 0 ratios were correlated with the gestational age or with the birth weight, in agreement with previous publications [11].

In the present study, we found that bFGF behaves differently from VEGF and TGF-beta1, in accordance with the fact that it is regulated differently [44]. In fact, no significant correlations were observed for the levels of this cytokine (or the ratios) with other molecules or variables, even if a significant fall ($p < 0.05$) in the ELF levels was observed in Dex-treated newborns.

A few earlier publications report quite varied data. In fact, an early TAF TGF-beta1 increase during the first week of life was found in premature newborns who developed CLD [2, 45], or was predictive of the need for oxygen therapy at home [37], but no significant effect of late (> 15 days of life) Dex treatment on the concentration of this cytokine was shown [45]. In contrast, in our patients Dex therapy was started earlier, on the 4th day of life, and this might explain the different results, suggesting that early treatment with Dex could influence the levels of this cytokine in TAF.

In addition, TGF-beta1 serum levels increased very early in extremely low gestational age newborns [46], and therefore it is mandatory to measure the concentration of this cytokine during the first days of life in order to evaluate a possible effect of Dex.

Pulmonary lavage VEGF levels [11] were found to be significantly higher on day 7 after birth in infants treated with two doses of Dex (0.5 mg/kg) at 12 and 24 hours of age than in control infants. This result was not seen in our study with four similar doses administered on the 4th day of life, suggesting that the

amount and the schedule of the drug administered may be important in inducing early variations in fibrogenic cytokine concentrations. Moreover, Dex has been shown to block the hypoxia-induced increase in VEGF mRNA [9]. In CLD, hypoxia may increase VEGF expression while Dex therapy may block this synthesis [9].

From a clinical point of view, it is interesting to note that the three subjects affected by severe BPD were not treated with corticosteroids and that their TGF-beta1 values, determined 48 hours after starting the observation period, were higher than those of the remaining subjects, suggesting that TGF-beta1 production may be related to or predictive of the clinical outcome, even if the data presented may only suggest and not demonstrate a causative relationship. This idea is further supported by the significant correlations observed between the TGF-beta1 ratios and both the extubation day and the Cdyn value ratios. Reduced lung inflammation and fibrosis induced by the steroids in our patients are the most likely mechanisms by which they produced a rapid improvement in lung function, with faster weaning from mechanical ventilation.

Pulmonary function test could be sensitive and specific in evaluating alveoli and airway conditions. Local flogosis with edema and exudates in the alveoli, peribronchial fibrosis and airways lesions plays the main role in the development of BPD, and for this reasons the grade of loss in elasticity of the lung (measured by the Cdyn) and/or the severity of airway lesions (measured by the resistance) could be correlated to the degree of inflammation and/or fibrosis. Our study suggests that in the first week of life, extremely low birth weight infants who subsequently develop BPD have significantly higher respiratory resistance than infants who do not, in agreement with previous studies [47]. Our results support therefore the hypothesis [47] that early pathological changes linked to BPD are already present in the first week of life.

Finally, the increased levels of TGF-beta1 observed in patients with BPD support a role for this cytokine in disease development, as previously indicated [2].

To our knowledge, this is the first report describing a significant effect of Dex on TGF-beta1 (and similarly on VEGF and bFGF) concentrations in ELF of preterm babies, together with a significant Cdyn improvement, this latter effect having been already described [14, 15].

CONCLUSION

In conclusion, the early dexamethasone treatment of premature newborns reduces the ELF concentrations of TGF-beta1 and bFGF, mediators known to be involved in fibrogenesis that, in turn, modify lung function. Further experimental and clinical studies and more subjects are necessary to further analyse the clinical usefulness of the findings presented in this report in terms of prediction of clinical outcome or possible therapy.

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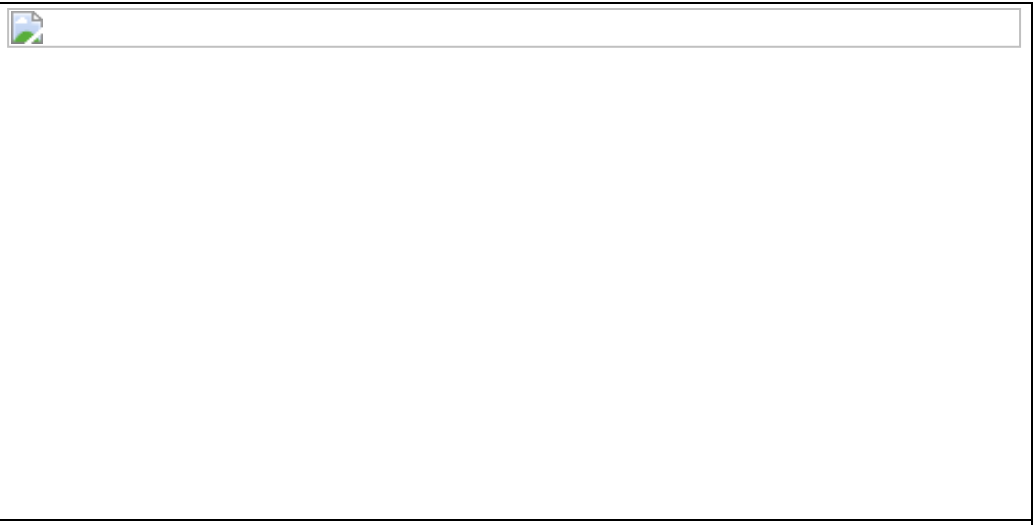
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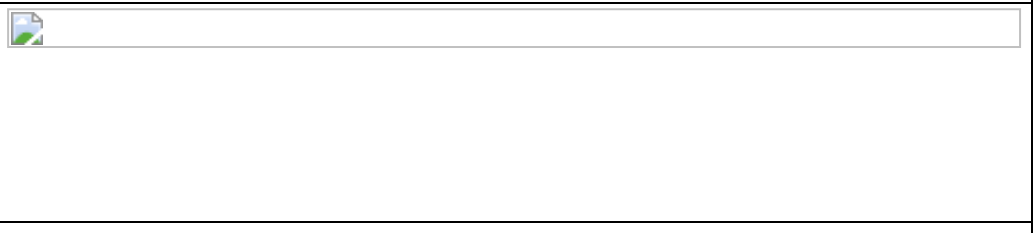


Table 1
Baseline characteristics of the preterm infants included in the study

Variables	Dexamethasone group (n = 10)	Control group (n = 10)
Gestational age (weeks)	27.9 ± 1.2	27.0 ± 1.2
Birth weight (g)	890 ± 158	812 ± 140
Small for gestational age	3 (30)	3 (30)
Sex ratio (male/female)	4/6	5/5
Antenatal steroids	6 (60)	6 (60)
Caesarean section	8 (80)	6 (60)
Respiratory distress syndrome	9 (90)	9 (90)
Obvious ductus arteriosus	2 (20)	2 (20)
Intraventricular haemorrage > 2°	2 (20)	1 (10)

Values are expressed as mean values ± SD or number and (percent).

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