OPIS PRZYPADKU

Dexamethasone therapy of chronic lung disease in pre-term infant

Zastosowanie Dexametazonu w leczeniu przewlekłej choroby płuc u wcześniaka

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ABSTRACT

The case of preterm, male infant (27 Hbd) with extremely low birth weight (868 g) and Respiratory Distress Syndrom is presented. Despite prolonged artificial ventilation (with High Frequency Oscillation Ventilation and FiO2 =100%), dopamine continuous iv infusion) on 30th day of life he started to deteriorate dramatically and the risk of chronic lung disease appeared. On the 32nd day of life Dexamethasone therapy was started. Post initial therapy his condition began improving clearly. This resulted in a successful extubation on the seventh day of Dexamethasone treatment. Breathing with C-PAP (FiO2=34%, Sa02 = 100%) was started. Dexamethasone was gradually reduced, its total cumulative dose was 4.52 mg/kg. The revision of bibliography related with corticosteroids application in preterm infants with chronic lung disease is presented.

KEY WORDS
Preterm infant, chronic lung disease, dexamethasone

STRESZCZENIE

Zaprezentowano przypadek wcześniaka płci męskiej (Hbd 27) z niską masą urodzeniową (868 g), u którego wystąpiły objawy zespołu zaburzeń oddechowych. Stosowano przedłużoną wentylację mechaniczną (również z zastosowaniem High Frequency Oscillation Ventilation z FiO2100%, ciągłą dożylną infuzją dopaminy), w 30 dniu życia jego stan zaczął się dramatycznie pogarszać i pojawiło się podejrzenie przewlekłej choroby płuc. W 32 dniu życia rozpoczęto stosowanie Dexametazonu. Już po rozpoczęciu leczenia zaobserwowano bardzo istotną poprawę w stanie zdrowia dziecka, co umożliwiło jego ekstubację w 7-mym dniu terapii i zastosowanie CPAP z FiO2 =34% uzyskując SaO2=100%. Dexametazon stopniowo odstawiono a jego całkowita dawka wyniosła 4,52 mg/kg. W pracy przedstawiono przegląd piśmiennictwa dotyczący zastosowania sterydoterapii u wcześniaków z przewlekłą chorobą płuc.

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Ann.Acad.Med.Siles. 2009, 63, 6, 86-90

ISSN 0208-5607

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Wcześniak, przewlekła choroba płuc, dexamethason

INTRODUCTION

For many years dexamethasone has been used to prevent and treat Chronic Lung Disease (CLD). The anti-inflammatory effect of steroids improved lung function but as it was often administered in very high doses and for a long time it was also toxic for developing brain causing neurological impairment (1). Controversy was aired when data about the increased rate of Cerebral Palsy (CP) and gastrointestinal perforations was published. Authorities recommended against the use of corticosteroids (2). However, it is important to notice that the trials that caused the concerns analysed mostly early steroid therapy.

The aim of this report, inspired by the case of the presented neonate is to answer the question whether late (>7 days of life) dexamethasone therapy can wean neonates off ventilators and reduce the oxygen support of pre-term infants at high risk of CLD, and to discuss it's influence on CP rate and mortality.

CASE REPORT

Premature, male neonate was born in 27 Hbd, weighing 0.868kg as a second dichorionic diamniotic twin. Mother before labour received corticosteroid therapy to prevent RDS syndrome in child. His APGAR score was 5/8. He received 2 doses of surfactant after birth without spectacular improvement. He was admitted to the Intensive Care Unit (ICU) with prematurity, extremely low birth weight and Respiratory Distress Syndrome (RDS) which was confirmed by a radiological picture. No laboratory examinations confirmed perinatal sepsis although later multiple episodes of sepsis were confirmed in blood cultures treated accordingly to obtained microbiological tests (Staphyloccocus: aureus, coagulase negative, capitis as well as candida albicans). He remained ventilator dependent , with 7 day period of spontaneous breathing in the second week of life (with application of nasal CPAP and FiO2 =0,4). On the 30th day of live he was beginning to deteriorate dramatically. On the basis of Bancalari criteria CLD was diagnosed. CNS hemorrhage, presence of hemodinamicaly significant Patent Ductus Arteriosus and anemia were excluded. He was treated with continous intravenous infusion with dopamine (10-15 mcg/kg/min) but was still hypotensive (mean BP 28-36 mmHg). Ventilation support was increased with High Frequency Oscillation Ventilation at average of 13-14 H2, delta P 20-24 cm H2O and FiO2=100%. Despite this oxygen saturations predominantly remained below 80%. Corticosteroid therapy was started according to the usual protocol. Dexamethasone was given on the 32nd day of life twice a day 0.25 mg/kg for 7 days, 0.11 mg/kg for 3 days and 0.06 mg/kg for 3 days - total cumulative dose 4.52 mg/kg . Post initial therapy his condition began to improve clearly. This resulted in successful extubation on the seventh day of treatment. Breathing with C-PAP (FiO2=34%) was started. Sa02 was than 100%. His steroid dose was being gradually reduced. Hypertension was noticed as a short side effect. This was controlled with nifedipine and disappeared after weaned from corticosteroid therapy. At second month of age rethinopathy grade 2 with pluse was diagnosed, needed 1 course of laser therapy.The child was discharged home 26 weeks after admision, after 114 days treatment in ITU. In follow-up generalized developmental delay was observed, treated by rehabiltation in child development center.

DISCUSSION

Is Dexamethasone Really Helping?

One of the most important Cochrane systematic reviews regarding the topic of late postnatal corticosteroids was prepared by Halliday at al.(3). Their study included 19 randomised controlled trials from 1966 to May 2008 and analysed short-term and long-term outcomes. Preterm neonates with or developing CLD, defined as oxygen dependent and/or ventilator dependent, and with or without radiographic changes of bronchopulmonary dysplasia (BPD) were eligible so including criteria was not very restricted.

Results of this study prove that dexamethasone can acutely improve lung function as happened in presented case. Mortality was reduced at 28 days (typical relative risk RR 0.49 95%CI 0.28, 0.85) with number needed to treat (NNT) 17 (95%CI 10 to 100).
Chronic lung disease, observed at 28 days (RR 0.87) and at 36 weeks' PMA (RR 0.72) were also significantly decreased as well as the need for home oxygen both in overall and in specific groups of survivors. Moreover steroid therapy significantly increased successful extubation at three, seven and 28 days. It is important to notice that the mortality at discharge or latest reported age did not change.
Among the short-term complications, the risk of hyperglycaemia, glycosuria and hypertension was increased but there was no significant difference between the groups in gastrointestinal sequelae. The study also analysed long-term adverse neurological effects. The rate of cerebral palsy at the latest reported age was not significantly increased, neither was overall (53 out of 382 infants in steroid group (~14%) vs 43 out of 374 infants in control group (~11,5%), RR 1.22 95%CI [0.84;1.77]), nor in studies limited to the first 3 years of life (56 out of 393 infants in steroid group (~14%) vs , RR 1.14 95%CI [0.79;1.64]).
Unfortunately there was a significant risk of bias in included studies that question methodological quality especially when long-term adverse neurodevelopmental effects are concerned. There was no follow up at all in seven studies, and in two trials follow up rate was very low (32%, 56 %).
In six studies out of 12 follow up was not longer than 36 months. This is important, as diagnosis of CP is not always certain before five years of age. Moreover, criteria for the diagnosis of cerebral palsy were not specified in seven trials. It is also difficult to interpret the results because infants were exposed to a different cumulative dose of dexamethasone: initial doses were 0.5-0.10 mg/kg/day but the time of therapy varied between three days up to six weeks and some patients in control trials were given open-label steroids (of a different "contamination" rate).

Maybe A Smaller Dose of Dexamethasone Can Be Used?

One of the trails(4) enrolled in the Doyle at al Cochrane collaboration meta- analysis, focused on assessing whether a lower dose of dexamethasone could facilitate extubation. Initially the study's aim was to show the long-term effects of steroid therapy and it's influence on survival. However, unfortunately, the trail was terminated because of the limited enrollment. Finally, only 70 infants (10% of the planned sample size) were analysed. However this was a randomised, double blinded trail and it's methodological quality was high.
Only children at high risk of developing CLD, who were ventilator dependent after the first week of life, (GA <28 weeks or extremely low birth weight <1000 g) met the eligible criteria. Dexamethasone was given twice-daily as follows: 0.15mg /kg per day for three days, 0.1 mg/kg per day for three days, 0.05 mg/kg per day for two days and 0.02 mg/kg per day for a further two days. A course of the same-blinded drug (dexamethasone or 0.9% saline placebo) could be repeated if the infant's condition required more intense therapy. The total cumulative dose of one course was 0.89mg/kg over 10 days. This is five times less than the protocol that presented patient received.
The results are reassuring. More infants were extubated successfully ($p<0.001$) by 10 days in the dexamethasone group (60%) comparing to control (12%). These results were quite similar to data from Cochrane reviews(3), where by the 7th day of therapy 48% of infants in the steroid group and 20% in the placebo group were successfully extubated.
Moreover, ventilator and oxygen requirements improved over the 10 days (mean airway pressure, the peak inspired pressure and the Fi02 all decreased significantly) and duration of intubation was also shorter. There was no relevant difference between the groups in blood pressure, glucose concentrations or other complications so short time adverse effects were eliminated.
However, there was also no significant difference in mortality and rates of BPD among infants who survived to a corrected age of 36 weeks, or in the proportion of infants who went home with oxygen so, in that aspect, therapies with higher doses(3) seem to be more efficient.

How is the Risk of Chronic Lung Disease Connected with Mortality and Cerebral Palsy?

The next meta-analysis(5) examined in depth the hypothesis that the level of risk for CLD modifies the effect of corticosteroids and it's impact on cerebral palsy and mortality. The inspiration for the study was the fact that the children with CLD who

were not treated with steroids had worse neurodevelopmental outcome than similar infants without CLD.

Twenty randomised controlled trials of postnatal corticosteroids in pre-term infants that reported rates of both mortality and CP met eligibility criteria. In the group of 1721 infants enrolled, 433 died before follow up and among the rest examined (followed up rate was 89%) 220 were diagnosed with CP. It is not specified in what rate dexamethasone, bethametasone and hydrocortisone were used in the trials so it may confound the results, although it can be assumed that dexamethasone, as the most popular, was used in the majority of studies.

Meta-analysis showed that late steroid treatment had no significant effect on death before latest follow up (18.7% in the steroid group vs 20.8% in the placebo, RR 0.87, RD [- 0.03]) so it confirms the results of the Cochrane review(3). CP rate among survivors was significantly increased when early and late therapy were analysed together, and there was trend in that direction when only late treatment was considered (20.8% vs 17.1%, RR 1.16 [95%CI, 0.81(sic!) to 1.66] , RD 0.03 [95%CI, -0.04 to 0.09]). However, it is important to notice that there was no significant effect of corticosteroid treatment on the combined rate of mortality or CP either when later (RR 0.99 [95%CI 0.81 to 1.21] RD 0.00 [95%CI -0.07 to 0.06]) or early therapy was analysed.

The data could be understood that, generally with steroid treatment, children may be at higher risk to suffer from neurodevelopmental adverse effects but as well have slightly improved chances of survival (although reduction in mortality is statistically non-significant).

Another very significant result is the relationship between combined outcome, death or CP, and the risk for CLD (defined as the rate of CLD in the control group). For every 10% that the rate of CLD increased in the control group the Risk Difference (RD) between the groups for death or Cerebral Palsy decreased by 3.8 %. Analysis of the regression line showed that if the rate of CLD was below 35%, steroid treatment significantly increases the chance of death or CP, whereas if the risk for exceeds 65%, it reduces this chance. These results show that the group of premature infants at the highest risk of CLD can benefit from treatment.

There are similar potential confounding variables in this meta-analysis as in the first study analysed(3). It includes a different time of initiating treatment, contamination rate of control group (median 33%), cumulative dose of drug (median 3mg/kg), follow up rate (sometimes < 90%), a time of follow up and assessment, not always by experts. However authors claim that none were significantly related to the corticosteroid effect on death or CP, and the risk for CLD.

This trial confirms that the children at high risk for CLD are more favorable to benefit from the corticosteroid therapy, and that there is a point above which the benefits overweigh the risks. The biggest limitation in application of these results into clinical practice is difficulty in showing this point because there is no objective measure in how to accurately predict CLD in populations at high risk (in the study it was done retrospectively).

CONCLUSIONS AND INDICATIONS FOR FUTURE PRACTICE

According to the above described case late dexamethasone therapy can facilitate extubation, reduce the rate of BPD and need of oxygen. From the other hand it was proven that it doesn't improve overall mortality (3). One trial suggests also that short time beneficial effect might be achieved even when much smaller doses of drug than in the standard protocol are used (4). None of the studies have been designed to assess long term adverse effects of treatment on neurodevelopment; so available data is incomplete and carries some risk of confounding (3,5), even though there is no strong evidence that late dexamethasone therapy increases the rate of CP (3,5).

Owing to the concerns about long-term adverse effects the use of post-natal steroids have decreased over the last 10 years but consequently the rate of BPD increased in the most pre-term infants for whom protracted ventilation itself could be detrimental (1). It is probable that corticosteroids were not used in some infants who might have benefit (5). The lack of randomised, placebo controlled, double blinded studies assessing the long-term neurodevelopmental effects make it reasonable to restrict the use of dexamethasone to the group of infants at the highest risk of developing CLD, but the concerns about Cerebral Palsy should not withdraw the decision to start the treatment in critically ill pre-terms with respiratory failure, who otherwise cannot be weaned off the ventilator.

ACKNOWLEGMENTS

This paper was realized as part of an Evidence Based Neonatology course at the Peninsula Medical School (GB) under supervision from Dr Michael Quinn and Dr Kalyaraman Kumaran. I would like to express my gratitude for their help and stimulation to prepare this manuscript.

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