ORIGINAL ARTICLE

Less postnatal steroids, more bronchopulmonary dysplasia: a population-based study in very low birthweight infants

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Objective: To study the association between reduced use of postnatal steroids for bronchopulmonary dysplasia (BPD) in very low birthweight (VLBW) infants and oxygen (O₂)-dependency at 28 days of age and at 36 weeks postmenstrual age.

Design: Large national database study.

Setting: The Israel National VLBW Neonatal Database.

Patients: The sample included infants born between 1997 and 2004, of gestational age 24–32 weeks, who required mechanical ventilation or O₂ therapy. Four time periods were compared: 1997–8 (era 1, peak use), 1999–2000 (era 2, intermediate), 2001–2 (era 3, expected reduction) and 2003–4 (era 4, lowest). The outcome variable "oxygen dependency" was based on clinical criteria. Multivariate regression models were used to account for confounding variables.

Results: Steroid use fell significantly from 23.5% in 1997–8 to 11% in 2003–4 ($p < 0.005$). After adjustment for relevant confounding variables, the odds ratio for O₂ therapy at 28 days in era 4 versus era 1 was 1.75, 95% confidence interval (CI) 1.47 to 2.09 and 1.41, 95% CI 1.15 to 1.73 at 36 weeks postmenstrual age. The mean duration of O₂ therapy increased from 25.3 days (95% CI 23.3 to 26.3) in era 1, to 28.0 days (95% CI 26.6 to 29.4) in era 4. Survival increased from 78.5% in era 1 to 81.6% in era 4 ($p < 0.005$).

Conclusions: The use of steroids has fallen considerably since the awareness of the adverse effects of this treatment. This change has been temporally associated with increased O₂ dependency at 28 days of age and at 36 weeks postmenstrual age. The prolongation of O₂ therapy was modest in degree.

The use of steroids for the prevention or treatment of bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD) in preterm infants has had fluctuating popularity throughout the history of modern neonatology.^{1–2} The power of this treatment derives primarily from the acute improvement in pulmonary mechanics that is often seen within a day or two of starting treatment. Indeed, meta-analyses of randomised controlled trials show that postnatal steroids may reduce both the incidence and severity of BPD.^{3–5} This potential benefit dovetails with the frustration experienced by many neonatologists who have been disappointed to witness the continuing incidence of BPD despite the therapeutic advances of antenatal steroids, postnatal surfactants and advanced techniques of ventilation.⁶ However, the impetus for the use of steroids has been tempered by the emergence of data showing adverse short-term and long-term effects associated with this treatment.^{7–10} Many of the data on adverse effects appeared mainly during the years 1998–2001 and led to the publication in 2001–2 of new clinical guidelines for postnatal steroid treatment by the European Association of Perinatal Medicine and by Committees for the Fetus and Newborn of the American Academy of Pediatrics and the Canadian Pediatric Society.^{11–12} According to the guidelines, steroids should not be used routinely for prevention or treatment of BPD, but only in "exceptional clinical circumstances" and after informing the parents. The need for more research, particularly with long-term follow-up, was emphasised.

Since 1998, databases on very low birthweight (VLBW) infants have observed that there has been a progressive reduction in the use of postnatal steroids (B. Reichman personal communication, 2005).¹³ We hypothesised that, by using fewer steroids, there would be a relative increase in the incidence or severity of BPD.

The aims of this population-based study were to evaluate trends in postnatal steroid use for BPD and to correlate the

changes with the incidence of oxygen (O₂) dependency at 28 days of age and at 36 weeks postmenstrual age (PMA), with due adjustment for relevant confounding variables.

METHODS

Israel's National VLBW Infant Database

The database procedures have been described in detail elsewhere.¹⁴ Briefly, infants with a birth weight of ≤ 1500 g who are born alive in all of the country's 28 neonatal units are included in the database. Data are prospectively collected on a prestructured form and include parental demographic information, maternal pregnancy history and antenatal care, mode of delivery, infant's status at birth, procedures and morbidity during hospitalisation, and outcome at discharge. Definitions used were concomitant with those of the Vermont–Oxford Trials Network; they were defined by the scientific committee before data collection and have remained unaltered since then.¹⁵ Once collected by the local investigators, the data are sent to the database coordinating centre, checked for missing items and logical errors, corrected, completed, and then entered into a computerised database. Patient information is cross-checked with the national birth registry, and data from any missing infant are requested from the birth hospital. The database comprises approximately 99% of all infants with VLBW in Israel. Data on all infants are collected until discharge home or death.

Definition of outcome variables

The diagnosis of BPD is problematic; there is much variation between units, and the newly developed "physiological definition" is not as yet widely applied.¹⁶ Thus, to maximise

Abbreviations: BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; PMA, postmenstrual age; VLBW, very low birthweight

consistency across the study sample, two surrogate outcome measures were used: O₂ dependency at 28 days of age and at 36 weeks PMA. PMA was calculated as gestational age at birth plus chronological age in completed weeks. The correlation between oxygen dependency and an assigned clinical diagnosis of BPD was >95%. Delivery room resuscitation included endotracheal intubation, cardiac massage or epinephrine administration. Respiratory distress syndrome was defined by characteristic clinical and radiographic findings.¹⁷

Study sample

For the purposes of this study, we included all infants with a birth weight of ≤1500 g and gestational age of 24–32 weeks, who required any oxygen or ventilatory assistance and thereby were at increased risk for BPD. Infants who died in the delivery room or who had lethal congenital malformations were excluded from the sample. During the study period (1997–2004), 12 435 VLBW infants were included in the database, and, of these, 8566 met the study criteria. 1354 infants died before 28 days of age and 24 infants had missing data, leaving a final study sample of 7188 infants.

For the purposes of comparison, the study period was divided into four consecutive eras: era 1, 1997–8 (*n* = 1711 infants); era 2, 1999–2000 (*n* = 1788); era 3, 2001–2 (*n* = 1809); and era 4, 2003–4 (*n* = 1880), on the basis of previous data that had suggested that the peak of steroid use had been in 1998 (Reichman B, personal communication, 2005).

Statistical analysis

The incidence of each of the major variables (O₂ dependency at 28 days and at 36 weeks PMA, and postnatal steroid administration) in each time period was compared using the χ^2 test for linear trend. Multivariate logistic regression analysis was used to assess the independent effect of eras 2, 3 and 4 compared with era 1 on O₂ dependency at 28 days and at 36 weeks PMA after adjustment for possible confounding factors, such as maternal hypertensive disorders, ethnic origin, antenatal steroid treatment, gestational age, small for gestational age status, multiple pregnancy, mode of delivery, resuscitation at birth, sex and respiratory distress syndrome. Differences in duration of oxygen therapy between the time periods were tested using general linear regression models. Statistical analyses were carried out using the SAS statistical software V.9.1.3.

RESULTS

Outcome variables

Among the study sample of 7188 infants, the mortality decreased from 21.5% (368/1711) in 1997–8 to 19.2% (343/1788) in 1999–2000, 18.6% (336/1809) in 2001–2 to 18.4% (346/1880) in 2003–4 (*p* < 0.005). As shown in fig 1, the incidence of O₂ therapy at age 28 days rose from 29.1% in era 1 to 38.6% in era 4 (*p* < 0.001). O₂ dependence at 36 weeks rose from 12.9% in era 1 to 18.7% in era 4 (*p* < 0.001). Postnatal administration of steroids fell from 23.5% in era 1 to 11% in era 4 (*p* < 0.001).

Table 1 shows the clinical characteristics of the infants in the four time periods. Early prenatal care and antenatal steroid treatment increased and less infants required resuscitation in the delivery room over the study period. In addition, the proportion of infants of lower gestational age (<28 weeks) rose slightly between eras 1 and 4.

Multiple logistic regression analyses assessed the influence of the study era on the need for O₂ therapy at 28 days of age and at 36 weeks PMA after adjustment for the relevant potential confounders (table 2). In this analysis, oxygen therapy at both 28 days and 36 weeks was significantly raised in era 4 as compared with era 1 (odds ratio (OR) 1.75, 95% confidence

Figure 1 Incidence of oxygen dependency at age 28 days and at 36 weeks postmenstrual age and postnatal steroid treatment over the four study eras.

interval (CI) 1.47 to 2.09 at 28 days and OR 1.41, 95% CI 1.15 to 1.73 at 36 weeks).

Duration of O₂ therapy

The increase in the risk of O₂ requirement at 36 weeks was reflected in only a modest increase in the overall duration of O₂ therapy in the whole population (table 3). After adjustment for the relevant confounders, there was a rise in the mean duration of O₂ therapy from 24.8 days (95% CI 23.3 to 26.3) in era 1 to 28 days (95% CI 26.6 to 29.4) in era 4 (*p* < 0.05).

The duration of O₂ therapy was also considered in three mutually exclusive groups of infants: those with no BPD, those receiving O₂ at 28 days, and those still on O₂ therapy at 36 weeks PMA. After adjustment for confounders, a mean increase of <2 days was noted in the 28-day group, whereas a reduction of 10 days was seen in the 36-week group. No change was seen in the duration of mechanical ventilation between the study periods (data not shown).

Highest risk group

We repeated all of the above analyses in the subset of highest risk infants of gestational age <28 weeks. The findings were essentially unchanged (data not shown).

DISCUSSION

This study has shown, in a large, population-based sample of VLBW infants, that the reduction in the use of postnatal steroids was associated with a 1.7-fold increase in oxygen dependency at 28 days of age and a 1.4-fold increase at 36 weeks PMA. However, the magnitude of the increase in duration of O₂ therapy was modest.

There are certain limitations to this study that need to be considered. Firstly, no data were available on the type of steroid (dexamethasone, hydrocortisone, budesonide, etc), dose, mode of administration (intravenous or inhaled) and duration of therapy. It has been reported that many neonatologists are using shorter courses and lower doses of steroids,^{18 19} and thus the overall reduction in the quantity of steroids given may be much greater than that estimated by this study. Likewise, the timing of steroid treatment may have changed, which was not assessed in this sample. Clinicians might also be wary of using early steroids and prefer to wait until the infants meet the definition of "exceptional clinical circumstances" as defined in the guidelines of the American Academy of Pediatrics and the Canadian Paediatric Society. As the Cochrane meta-analyses suggest that delayed treatment is the least efficacious timing,

Table 1 Clinical characteristics of infants in the four study time periods

Variables	Era 1 1997–1998 (n = 1711)	Era 2 1999–2000 (n = 1788)	Era 3 2001–2002 (n = 1809)	Era 4 2003–2004 (n = 1880)	p Value
Male sex	911 (53.2)	924 (51.7)	910 (50.3)	1028 (54.7)	NS
Ethnic origin (non-Jewish)	434 (25.4)	487 (27.2)	494 (27.3)	555 (29.5)	<0.05
Start of prenatal care ≤ 12 weeks	1384 (80.9)	1491 (83.4)	1568 (86.7)	1613 (85.8)	<0.001
Antenatal steroids					<0.05
Full	839 (49)	984 (55)	968 (53.5)	1003 (53.3)	
Partial	333 (19.5)	321 (17.9)	320 (17.7)	368 (19.6)	
BW < 1000 g	617 (36.1)	649 (36.3)	670 (37.8)	694 (36.9)	NS
GA ≤ 28 weeks	803 (46.9)	847 (47.4)	891 (49.2)	925 (49.2)	NS
SGA	258 (15.1)	266 (14.9)	249 (13.8)	300 (16)	NS
Multiple birth	751 (43.9)	758 (42.4)	747 (41.3)	774 (41.2)	NS
Caesarean section	1183 (69.1)	1238 (69.2)	1303 (72)	1407 (74.8)	<0.001
DR resuscitation	953 (55.7)	936 (52.4)	868 (48)	853 (45.4)	<0.001
RDS	1274 (74.5)	1398 (78.2)	1380 (76.4)	1500 (79.8)	<0.01
Surfactant	1057 (61.8)	1129 (69.1)	1113 (61.5)	1169 (62.2)	NS

BW, birth weight; DR, delivery room; GA, gestational age; NS, non-significant; RDS, respiratory distress syndrome; SGA, small for gestational age.

Table 2 Multiple logistic regression analysis of effect of study time period on oxygen requirement at 28 days and 36 weeks postmenstrual age

	97–98 vs. 99–00 OR (95% CI)	01–02 OR (95% CI)	03–04 OR (95% CI)
O ₂ 28 days	1.07 (0.89 to 1.28)	1.42 (1.18 to 1.70)	1.75 (1.47 to 2.09)
O ₂ 36 weeks	0.90 (0.72 to 1.12)	1.48 (1.21 to 1.82)	1.41 (1.15 to 1.82)

Values are given after adjustment for start of prenatal care, maternal hypertension, ethnic origin, antenatal steroid therapy, multiple births, mode of delivery, resuscitation in the delivery room, appropriateness for gestational age and respiratory distress syndrome.

Table 3 Duration (mean days (95% CI)) of O₂ therapy in all infants and separated by the outcome variable groups

	Era 1 1997–8	Era 2 1999–2000	Era 3 2001–2	Era 4 2003–4	p Value
All infants	25.3 (23.3, 26.3)	26.1 (24.3, 27.2)	28.6 (26.8, 29.3)	28 (26.6, 29.1)	1 v. 3, 1 v. 4, 2 v. 4: <0.05
O ₂ < 28 days	7 (6.5 to 7.4)	7 (6.5 to 7.5)	7.3 (6.8 to 7.8)	7.5 (7.0 to 8.0)	NS
O ₂ 28 days	40.5 (38.6 to 42.6)	41.6 (39.8 to 43.5)	42.6 (40.7 to 44.5)	42.2 (40.5 to 43.9)	NS
O ₂ 36 weeks	92.3 (86.3 to 98.3)	92.0 (86.2 to 97.8)	86.6 (81.7 to 91.5)	82.1 (77.4 to 86.9)	1 v. 4: <0.05, others: NS

NS, non-significant.

Values are given after adjustment for start of prenatal care, maternal hypertension, ethnic origin, antenatal steroid therapy, multiple births, mode of delivery, resuscitation in the delivery room, appropriateness for gestational age and respiratory distress syndrome.

the potential benefits of steroid treatment may be at present squandered.

Previous studies have shown that the diagnosis of BPD varies markedly between centres, and this may reflect diagnostic criteria and nursery practices relating to the administration of O₂. In our study, no data were available regarding O₂ saturation targeting during the study period. A physiological definition of BPD based on a challenge of room air breathing at 36 weeks gestational age with defined O₂-saturation targets has been shown to reduce the incidence of the diagnosis and also to decrease the variation between units.¹³ This definition is not as yet widely available.

Ever since the recognition of the risks associated with high-dose, early dexamethasone treatment, alternative approaches to the treatment of BPD have been used. Hydrocortisone has been an attractive possibility since the demonstration of transient adrenocortical insufficiency in preterm infants, particularly after exposure to chorioamnionitis.^{20–22} A pilot study suggested that a tapering course of a low dose over 12 days was associated with reduced risk for BPD. However, unfortunately, two large

randomised controlled trials failed to confirm any marked benefits, and so both hydrocortisone and dexamethasone were stopped prematurely because of increased incidence of gastrointestinal perforation in treated infants.^{22–23} Lower doses of dexamethasone (0.1–0.2 mg/kg/day) have been shown to have beneficial effects on lung mechanics that were similar to those seen with higher doses.^{24–26} However, to date, follow-up data to support a formal recommendation for this intervention have been insufficient.

Alternative approaches to the treatment of BPD that have been studied include vitamin A,²⁷ recombinant human copper-zinc superoxide dismutase,²⁸ α-1-antitrypsin²⁹ and n-acetylcysteine.³⁰ Of these, the only treatment shown to have produced a marked reduction in BPD is that with vitamin A. However, the modest degree of this effect, with the required prolonged parenteral course of treatment, has limited the popularity of this intervention.

The central question of this study has also been dealt with in a recent study that, to date, has been reported only in abstract form. This study, carried out in three large VLBW neonatal

What is already known on this topic

- Postnatal steroids ameliorate the severity of bronchopulmonary dysplasia.
- Postnatal steroids are associated with increased risk for neurodevelopmental impairment, including cerebral palsy.

What this study adds

- The use of postnatal steroids has fallen dramatically in recent years.
- Reduced use of steroids is associated with increased oxygen dependency at 28 days and at 36 weeks postmenstrual age, but the increase in duration of oxygen therapy is modest.

networks, showed markedly reduced use of steroid treatment between 2001 and 2003.¹³ Unadjusted assessment of the incidence of BPD and mortality showed no marked change over the study period.

In summary, marked reduction in steroid administration is associated with a 1.4–1.7-fold increase in O₂ therapy at 28 days of age and at 36 weeks PMA. Further studies are needed to identify those severely ill infants in whom the potential benefits of steroid treatment in reducing BPD and its associated neurodevelopmental impairment may exceed the risks associated with steroid treatment.³¹

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