SHORT REPORT

Neonatologists are using much less dexamethasone

E S Shinwell, M Karplus, D Bader, S Dollberg, I Gur, Z Weintraub, S Arnon, E Gottfreid, A Zaritsky, I R Makhoul, D Reich, L Sirota, I Berger, A Kogan, S Yurman, M Goldberg, D Kohelet

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Two historical cohorts (1993–1994 and 2001) of preterm infants ventilated for respiratory distress syndrome were compared. Dexamethasone administration fell from 22% to 6%. Chronic lung disease in survivors rose slightly from 13% to 17%, and mortality fell from 21% to 15% (other causes). The effect of restriction of dexamethasone use on chronic lung disease and mortality remains to be seen.

Recent evidence has suggested a causal relation between neonatal dexamethasone therapy and cerebral palsy and other neurodevelopmental sequelae.[1–4] As a result and in keeping with new guidelines from the American Academy of Pediatrics, many neonatologists have considerably restricted the use of steroids. Randomised trials of dexamethasone therapy have shown a modest beneficial effect on the incidence of chronic lung disease (CLD) without reduction in mortality.[5–11] Thus, the objectives of this study were to document the change in dexamethasone use by comparing two cohorts of preterm infants born during 1993–1994 and 2001. CLD and mortality were also examined.

METHODS

The two study cohorts were derived from 18 neonatal intensive care units in Israel. The first cohort (1993–1994) comprised infants (> 90% of eligible infants enrolled) from a randomised, placebo controlled trial of dexamethasone given on days 1–3 of life for the prevention of CLD.[12] The infants had a birth weight of 500–2000 g and were ventilated for respiratory distress syndrome. After the age of 7 days, open label steroids could be given. The study showed no effect on CLD or mortality.

The second cohort consisted of infants born in the same centres during the period 1 January to 31 May 2001, who would have met the same inclusion criteria as were used in the 1993–1994 study. This time period was chosen because of the publication of the major studies on the subject during 1999 and 2000.

CLD was defined as requirement for oxygen at 36 weeks postconceptional age, and the data for the 2001 cohort were collected by chart review in each centre and analysed using SPSS for Windows.

RESULTS

There was no significant difference in birth weight and gestational age of all infants and survivors between the two cohorts (table 1). There was a significant reduction in the use of all steroids ($p = 0.007$) and of dexamethasone in particular ($p = 0.001$) between the two time periods. In the 1993–1994 cohort, 22% of the infants were treated with open label dexamethasone after the age of 7 days, and the mean (SD) duration of treatment was 3 (1) days. In the 2001 cohort, only 6% received intravenous dexamethasone, and the mean (SD) duration of treatment was 0.5 (2) days. However, in this cohort, alternative forms of steroid treatment used included intravenous hydrocortisone, oral betamethasone, and inhaled budesonide in a variety of doses (0.1–0.5 mg/kg/day) and lengths of courses (3–32 days).

The incidence of death before discharge from the hospital fell from 21% to 15% ($p = 0.04$). The incidence of CLD in survivors rose slightly from 13% to 17%, but this finding was not significant ($p = 0.343$).

DISCUSSION

This retrospective historical cohort study shows a dramatic reduction in the use of postnatal dexamethasone therapy in neonatal intensive care units in Israel subsequent to the publication of reports of adverse neurological effects of this treatment. However, this has resulted in a clinical therapeutic

Table 1 Birth weight, gestational age, and incidence of the outcome variables in the two study cohorts

	1993–1994	2001	p Value
Number	248	312	
Birth weight (g)	1180 (35)	1160 (20)	0.575
Birth weight in survivors (g)	1260 (383)	1241 (391)	0.61
Gestational age (weeks)	28.8 (2.7)	28.6 (3)	0.249
Gestational age in survivors (weeks)	29.3 (2.6)	29.3 (2.7)	0.31
Steroid therapy	54 (22%)	41 (13%)	0.007
Dexamethasone (IV)	54 (22%)	20 (6%)	
Hydrocortisone (IV)	–	2 (1%)	
Betamethasone (PO)	–	5 (2%)	
Budesonide (inhaled)	–	20 (6%)	
Died	53 (21%)	46 (15%)	0.04
CLD in survivors (oxygen at 36 weeks)	33 (13%)	51 (17%)	0.343

Unless indicated otherwise, values are mean (SD).
IV, Intravenous; PO, by mouth; CLD, chronic lung disease.

dilemma for paediatricians faced with preterm infants with severe lung disease during the first weeks of life. The data shown here suggest that most clinicians adopt a policy of supportive treatment while reserving steroids for the sickest infants. When steroids are deemed to be necessary, some clinicians have chosen to replace intravenous high dose dexamethasone with lower doses and/or shorter courses of the same drug, and others have used alternative steroids, such as intravenous hydrocortisone, oral betamethasone, or inhaled budesonide. Support for each of these modes of steroid treatment can be found in a number of published studies in recent years.[13–16] However, none have acquired the status of established treatment.

In this small study, this change in prescribing habits has not resulted in significant changes in the incidence of CLD and mortality. However, in the absence of the relevant data required to rule out the many possible confounding variables, it is impossible to say whether the small increase in CLD represents a real absence of change or a type 2 error. In addition, the reduction in mortality probably reflects improvements in perinatal and neonatal care and is unrelated to the reduction in the frequency of postnatal administration of steroid.

Since the collection of data from the 2001 cohort, the American Academy of Pediatrics and the Canadian Pediatric Society have published guidelines for the use of postnatal steroid treatment.[17] These guidelines state that it should not be routine and should be limited to "exceptional clinical circumstances" such as an infant on maximal ventilatory and oxygen support. To further clarify the status of this problematic treatment, the academies have called for more randomised clinical trials in which the primary outcome variable should be survival without long term developmental impairments. No recommendations were made on alternative modes of steroid treatment.

In the early 1990s, steroid therapy for the prevention or treatment of CLD was the standard of care for very low birthweight infants. As can be seen from this study and from the recommendations of the American Academy of Pediatrics/ Canadian Pediatric Society, the pendulum has swung far in the opposite direction. If the results of this study are borne out by subsequent research, the pendulum may never swing back and steroids may attain the historical legacy of another unfortunate interlude in the history of neonatology.

CONTRIBUTORS

Dr E S Shinwell and Dr M Karplus designed the study. All other authors approved the study design, collected the data, reviewed the manuscript before submission for publication and approved the changes after review.

Authors' affiliations

E S Shinwell, Kaplan Medical Center, Rehovot, Israel
M Karplus, Soroka Medical Center, Beersheva, Israel
D Bader, Bnei Zion Hospital, Haifa, Israel
S Dollberg, Sourasky Medical Center, Tel Aviv, Israel
I Gur, Bikur Holim Hospital, Jerusalem, Israel
Z Weintraub, Carmel Hospital, Haifa
S Arnon, Meir Hospital, Kfar Saba, Israel
E Gottfreid, Ziv Hospital, Tsfat, Israel
A Zaritsky, Barzilai Hospital, Ashkelon, Israel
I R Makhoul, Rambam Hospital, Haifa
D Reich, Ha'emek Hospital, Afula, Israel
L Sirota, Schneider Children's Hospital, Petach Tikva, Israel
I Berger, Western Galilee Hospital, Nahariya, Israel
A Kogan, Sheba Medical Center, Tel Hashomer, Israel
S Yurman, Hillel Yaffe Hospital, Hadera, Israel
M Goldberg, Assaf Harofe Hospital, Tsrifin, Israel
D Kohelet, Wolfson Hospital, Holon, Israel

Correspondence to: Dr Shinwell, Department of Neonatology, Kaplan Medical Center, PO Box 1, Rehovot, Israel; eric_s@clalit.org.il

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