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Published in:
Archives of Disease in Childhood: Fetal and Neonatal Edition

DOI:
10.1136/archdischild-2022-324179

Publication date:
2023

Effect of systemic hydrocortisone in ventilated preterm infants on parent-reported behavioural outcomes at 2 years' corrected age: follow-up of a randomised clinical trial

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/archdischild-2022-324179).

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Received 24 March 2022
Accepted 16 December 2022
Published Online First 2 January 2023

To cite: Halbmeijer NM, Onland W, Cools F, *et al*. *Arch Dis Child Fetal Neonatal Ed* 2023;**108**:F373–F379.

ABSTRACT

Objective To report the parent-reported behavioural outcomes of infants included in the Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants study at 2 years' corrected age (CA).

Design Randomised placebo-controlled trial.

Setting Dutch and Belgian neonatal intensive care units.

Patients Infants born <30 weeks' gestation and/or birth weight <1250 g, and ventilator dependent in the second week of life.

Intervention Infants were randomly assigned to a 22-day course of systemic hydrocortisone (cumulative dose 72.5 mg/kg; n=182) or placebo (n=190).

Main outcome measures Parent-reported behavioural outcomes at 2 years' CA assessed with the Child Behavior Checklist (CBCL 1½–5).

Results Parents completed the CBCL of 183 (70% (183/262)) infants (hydrocortisone group, n=96; placebo group, n=87). Multiple imputation was used to account for missing data. Infants with critically elevated T-scores (>55) were found in 22.9%, 19.1% and 29.4% of infants for total, internalising and externalising problems, respectively; these scores were not significantly different between groups (mean difference −1.52 (95% CI −4.00 to 0.96), −2.40 (95% CI −4.99 to 0.20) and −0.81 (95% CI −3.40 to 1.77), respectively). In the subscales, we found a significantly lower T-score for anxiety problems in the hydrocortisone group (mean difference −1.26, 95% CI −2.41 to −0.12).

Conclusion This study found high rates of behaviour problems at 2 years' CA following very preterm birth, but these problems were not associated with hydrocortisone treatment initiated between 7 and 14 days after birth in ventilated preterm infants.

Trial registration number NTR2768; EudraCT 2010-023777-19.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Dexamethasone reduces the incidence of bronchopulmonary dysplasia in very preterm infants, but is associated with adverse neurodevelopmental outcomes, including behavioural problems.

⇒ Hydrocortisone is increasingly used as an alternative for dexamethasone, but evidence on the long-term safety of hydrocortisone initiated after the first week of life is lacking.

WHAT THIS STUDY ADDS

⇒ This randomised controlled study shows that systemic hydrocortisone initiated in the second week of life is not associated with a clinically relevant difference in parent-reported behavioural outcomes at 2 years' corrected age.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further studies on long-term effects of postnatal steroids in very preterm infants should include behavioural outcomes in early childhood.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common complication in survivors of preterm birth.[1] It is associated with long-term pulmonary sequelae lasting into adulthood and an increased risk of adverse neurodevelopmental outcomes.[2] In particular, infants with the most severe form of BPD are at high risk for cerebral palsy, developmental delays, poor school performance, behavioural problems and low IQ in adolescence.[3–5] Systemic postnatal corticosteroids have been extensively investigated for the prevention and treatment of BPD.[6] Initial randomised controlled trials (RCTs) showed that dexamethasone was highly effective in reducing the incidence of BPD, but this drug has fallen out of favour because of a possible association with adverse neurodevelopmental outcome, including behavioural problems.[7 8] Observational studies of preterm infants treated with postnatal

dexamethasone reported more behavioural problems at school age,[9 10] whereas a retrospective study reported less adverse effects on behaviour and motor development at school age in infants treated with postnatal hydrocortisone compared with dexamethasone.[11] Given these concerns, the efficacy and safety of hydrocortisone to reduce the incidence of BPD is increasingly studied.[12 13]

The Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants (SToP-BPD) study is currently the only published large placebo-controlled RCT investigating the efficacy and safety of systemic hydrocortisone treatment initiated in the second week of life in invasively ventilated very preterm infants. This study showed that hydrocortisone does not reduce the risk of the combined outcome death or BPD at 36 weeks' postmenstrual age (PMA),[14] and is not associated with an increased risk for the combined outcome death or neurodevelopmental impairment (NDI) at 2 years' corrected age (CA).[15] In addition, within this combined outcome the separate component death was significantly reduced in favour of the hydrocortisone group. Since survivors of preterm birth are, besides NDI, also at high risk to encounter behavioural problems with attentional difficulties, anxiety and withdrawn behaviour being most prominent,[16 17] we report in this study the parent-reported behavioural outcomes at 2 years' CA assessed by the Child Behavior Checklist 1.5–5 years (CBCL 1½−5) of infants included in the SToP-BPD study.

METHODS

Study design and setting

This double-blind, placebo-controlled RCT was performed between 15 November 2011 and 23 December 2016 in 16 neonatal intensive care units in the Netherlands and Belgium.[14 15 18 19] Briefly, infants born at a gestational age (GA) less than 30 weeks and/or with a birth weight less than 1250 g who were ventilator dependent between 7 and 14 days after birth were randomly assigned to receive either systemic hydrocortisone (cumulative dose 72.5 mg/kg) or placebo for 22 days.[14]

Outcomes

Results of the analyses of the primary composite outcome death or BPD at 36 weeks' PMA, secondary outcomes until hospital discharge and the key long-term outcome at 2 years' CA have been published previously.[14 15] Follow-up assessments at 2 years' CA were performed between 18 April 2014 and 27 June 2019 by trained paediatricians, paediatric psychologists and paediatric physical therapists, all blinded for treatment allocation.

Prior to the 2-year follow-up visit, parents completed the CBCL 1½−5 (Dutch version) to report on the child's behaviour problems.[20] The CBCL 1½−5 consists of 100 questions in which parents indicate on a 3-point Likert scale (0= 'not true', 1='somewhat or sometimes true' and 2='very true or often true') to what extent behaviours are present, during the preceding 2 months. The CBCL 1½−5 provides a total problem score as well as two broadband scales (internalising and externalising behaviours), seven syndrome scales (emotionally reactive, anxious/depressive, somatic complaints, withdrawn behaviour, sleep problems, attention problems, aggressive behaviour) and five Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)-oriented syndrome scales (affective problems, anxiety problems, pervasive developmental, oppositional defiant and attention deficit/hyperactivity problems). A standardised T-score for all scales, based on Dutch-Belgian norms, was calculated and entered by the centres in the database. A higher score reflects more behavioural problems. The reliability and validity of the CBCL 1½–5 is higher than 0.85.[21] We also report the rate of infants with a T-score above 55, as scores above 55 are critically elevated and yet indicative for serious behavioural problems in need of intervention.[22]

Statistical analysis

A sample size calculation was performed for the primary outcome of the SToP-BPD study, the composite of death or BPD at 36 weeks' PMA, as previously described[18 19]; no additional power calculation for the evaluation of behavioural outcomes was performed. Data analyses were performed in the intention-to-treat population, including all randomised patients regardless of protocol deviations or use of open-label corticosteroids.[18] Descriptive statistics summarise the clinical and parental characteristics and outcome parameters.

The effect of hydrocortisone compared with placebo on total, internalising and externalising problems, syndrome and DSM-IV-oriented scales was analysed with a t-test and crude mean differences were calculated.

Group differences in the rate of infants with a T-score above 55 were investigated with a generalised linear model using a binomial distribution with identity link and the absolute risk difference was calculated. Logistic regression models were used to estimate ORs.

For the CBCL scores, 30% was missing. In addition, 43% of the data of the syndrome scales and 52% of the DSM-IV-oriented subscales were not routinely calculated by the centres, and were therefore not entered in the database. Assuming that data were missing at random, we used multiple imputation with chained equations to impute missing outcome data for the CBCL scores.[23] The following prespecified variables were used as predictor variables within the imputation approach: baseline variables (GA, birth weight, sex and multiple birth), postrandomisation variables (BPD diagnosis and severe brain injury), 2-year composite cognitive and motor scores on the Bayley Scales of Infant and Toddler Development, Third Edition, Dutch version (BSID-III-NL), parental education and multilingual environment. Fifty imputed data sets were generated with 50 iterations in SPSS V.26.0. Predictive mean matching was used as the imputation routine for continuous data. The analyses were pooled based on Rubin's rules.[23 24] We performed a sensitivity analysis on cases with complete questionnaire data only.

Of the 262 infants included in our data analysis, 103 received 'open-label' hydrocortisone during the study period: 34 infants in the hydrocortisone group and 69 infants in the placebo group. To evaluate the robustness of the effect of hydrocortisone on behavioural outcomes, we performed a sensitivity analysis using a multivariable linear regression model adjusted for open-label hydrocortisone use (yes or no). Furthermore, exploratory linear and logistic regression models analysed the effect of hydrocortisone versus placebo on behavioural outcomes in infants with severe BPD and/or infants with NDI at 2 years' CA.

No formal adjustments for stratification or multiple comparisons were made. Statistical analysis was performed in IBM SPSS Statistics for Windows, V.26.0 (IBM).

RESULTS

Of the 372 infants enrolled in this trial, 276 (74%) survived until 2 years' CA; 95% (262/276) of the surviving infants returned for follow-up at 2 years' CA. Prior to the 2 years' CA follow-up visit, for 183 infants parents completed the CBCL, 96 allocated to the hydrocortisone group and 87 to the placebo group (figure 1).

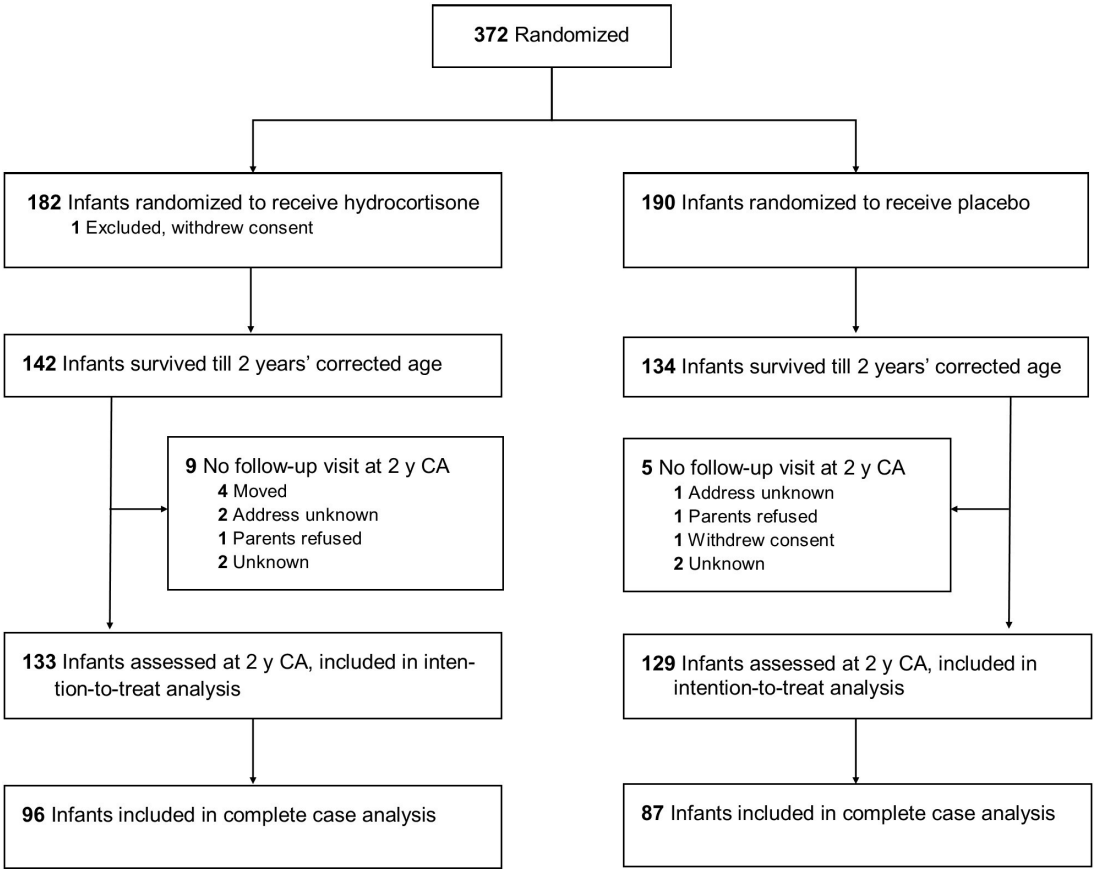

Figure 1 Consolidated Standards of Reporting Trials flow diagram. CA, corrected age.

Clinical characteristics of the 183 infants and their parents were similar in both groups with the exception of more multiple births and an overall higher level of parental education in the hydrocortisone group (table 1). Comparison of the clinical characteristics and outcomes of infants with and without a completed CBCL showed more multiple births, higher parental education, less multilingual environment, more moderate and severe BPD and less NDI at 2 years' CA in the group with a completed CBCL (online supplemental eTable 1).

Of the 183 completed checklists, the CBCL syndrome scales were calculated for 150 infants and the CBCL DSM-IV-oriented subscales for 126 infants. When multiple imputation was used to account for missing data, the T-scores for total, internalising and externalising problems were not significantly different between the hydrocortisone and placebo groups (crude mean difference for total problems T-score −1.52 (95% CI −4.00 to 0.96), for internalising problems T-score −2.40 (95% CI −4.99 to 0.20) and for externalising problems T-score −0.81 (95% CI −3.40 to 1.77)) (table 2). In both groups, high mean T-scores were found for the CBCL syndrome scales and DSM-IV-oriented subscales, but only the score for anxiety problems was significantly lower in infants treated with hydrocortisone compared with the placebo group (mean difference −1.26, 95% CI −2.41 to –0.12) (table 2).

Table 3 shows the proportions of infants with critically elevated behavioural problems defined as a T-score above 55. For the total, internalising and externalising problem scales, T-scores above 55 were found in 22.9%, 19.1% and 29.4% of infants, respectively. No differences were found between the hydrocortisone and placebo groups for the total, internalising and externalising problem scales, nor for the syndrome and DSM-IV-oriented subscales.

Sensitivity analyses with only cases with complete questionnaire data and adjusting for open-label hydrocortisone yielded similar results for the mean T-scores between both groups (online supplemental eTables 2 and 3). However, significantly lower proportions of infants with a T-score above 55 for anxiety problems and pervasive developmental problems were found in the hydrocortisone compared with the placebo group (online supplemental eTable 4).

Exploratory subgroup analyses of infants with severe BPD and/or infants with NDI at 2 years' CA revealed no significant effect of hydrocortisone on behavioural outcomes at 2 years' CA for both mean differences and group differences in percentages of infants with behavioural problems needing intervention (online supplemental eTables 5–8).

DISCUSSION

We found no significant differences in the parent-reported behavioural outcomes at 2 years' CA in invasively ventilated preterm infants treated with hydrocortisone or placebo initiated between 7 and 14 days after birth, except for a small reduction in anxiety problems in the hydrocortisone group. These results are consistent with the previously reported neurodevelopmental outcomes at 2 years' CA of the SToP-BPD study, assessed with the BSID-III-NL.[15]

Behavioural outcomes after treatment with postnatal steroids for BPD are rarely reported as outcome variable in RCTs. To our knowledge, this is the first double-blind, placebo-controlled RCT investigating the effect of hydrocortisone on behavioural

Table 1 Characteristics of infants and parents (n=183) with completed CBCL at 2 years' CA

	Hydrocortisone (n=96)	Placebo (n=87)
Infant birth characteristics		
Gestational age at birth, median (IQR), weeks	25.6 (25.0, 26.4)	25.6 (24.6, 26.6)
Birth weight, median (IQR), g	786 (670, 863)	740 (665, 865)
Male sex	51 (53.1)	54 (62.1)
Small for gestational age*	14 (14.6)	11 (12.6)
Multiple birth	40 (41.7)	27 (31.0)
Neonatal morbidities		
Moderate and severe bronchopulmonary dysplasia	65 (67.7)	61 (70.1)
Severe brain injury†	13 (13.5)	14 (16.1)
Infection‡	50 (52.1)	45 (51.7)
Severe retinopathy of prematurity, >grade 2	21 (21.9)	27 (31.0)
Neurodevelopmental outcomes at 2 years' CA		
Neurodevelopmental impairment§	36 (37.9)	35 (40.2)
BSID-III-NL		
Cognitive composite score, mean (SD)¶	95.7 (15.3)	94.8 (15.7)
Motor composite score, mean (SD)**	93.7 (13.6)	95.9 (15.2)
Neurological		
Cerebral palsy with gross motor function level >II	1 (1.0)	2 (2.3)
Sensory		
Severe visual impairment††	1 (1.0)	3 (3.4)
Hearing loss requiring hearing aids or deafness	1 (1.0)	1 (1.1)
Parental characteristics‡‡		
Parental education§§		
Low level	15 (15.6)	24 (27.6)
Middle level	32 (33.3)	28 (32.2)
High level	44 (45.8)	30 (34.5)
Unknown	5 (5.2)	5 (5.7)
Dutch as main language spoken at home	89 (92.7)	78 (89.7)
Multilingual environment	13 (13.7)	12 (13.8)

Data are n (%) unless stated differently.
*Defined as less than the 10th percentile on the Fenton growth chart.
†Includes infants with intraventricular haemorrhage >grade 2, cystic periventricular leukomalacia and posthaemorrhagic ventricular dilation during admission at the neonatal intensive care unit.
‡Includes infants with culture-proven sepsis and necrotising enterocolitis >stage 2a according to Bell classification during admission at the neonatal intensive care unit.
§Neurodevelopmental impairment was defined as presence of one or more of the following: cognitive and/or motor composite score less than 85 on the Bayley Scales of Infant and Toddler Development, Third Edition, Dutch version (BSID-III-NL); cerebral palsy greater than level II in the Gross Motor Function Classification System; or hearing or visual impairment.
¶For the cognitive composite score 88 infants in the hydrocortisone group and 77 infants in the placebo group were assessed.
**For the motor composite score 80 infants in the hydrocortisone group and 70 infants in the placebo group were assessed.
††Severe visual impairment is defined as blind or abnormal vision (limited vision, but the ability to see anything).
‡‡Parental characteristics at baseline are at the infant level (ie, parents were counted multiple times if they had multiple infants).
§§Parental educational level is defined as low if one or both parents have attended lower professional school or less or one parent low and the other middle; middle if both parents have attended medium professional school or one low and the other high; and high if one or both parents have attended higher professional school or university or one parent high and the other middle.
CA, corrected age; CBCL, Child Behavior Checklist.

Table 2 Behavioural outcomes assessed by CBCL 1.5–5 years at 2 years' corrected age

	Multiple imputation analysis		
	Hydrocortisone	Placebo	Mean difference (95% CI)*
CBCL			
Total problems	46.8 (10.4)	48.3 (10.5)	−1.52 (−4.00 to 0.96)
Internalising problems	45.1 (11.0)	47.5 (10.8)	−2.40 (−4.99 to 0.20)
Externalising problems	49.2 (10.4)	50.0 (11.5)	−0.81 (−3.40 to 1.77)
CBCL syndrome scales			
Emotionally reactive	52.3 (5.1)	53.0 (6.2)	−0.72 (−2.01 to 0.57)
Anxious/depressive	50.8 (2.6)	51.0 (2.8)	−0.24 (−0.83 to 0.35)
Somatic complaints	54.5 (7.7)	55.3 (8.1)	−0.83 (−2.72 to 1.07)
Withdrawn behaviour	53.8 (6.0)	54.3 (6.4)	−0.52 (−1.99 to 0.95)
Sleep problems	52.3 (5.7)	53.4 (7.3)	−0.64 (−2.19 to 0.90)
Attention problems	56.0 (8.7)	56.3 (8.6)	−0.25 (−2.28 to 1.77)
Aggressive behaviour	52.9 (5.5)	53.6 (7.2)	−0.71 (−2.23 to 0.80)
CBCL DSM-IV-oriented subscales			
Affective problems	53.9 (6.1)	53.9 (5.3)	0.04 (−1.29 to 1.37)
Anxiety problems	51.3 (3.8)	52.6 (5.8)	−1.26 (−2.41 to 0.12)†
Pervasive developmental	53.8 (7.0)	54.7 (7.3)	−0.92 (−2.59 to 0.75)
Oppositional defiant problems	53.6 (6.0)	54.0 (6.7)	−0.34 (−1.75 to 1.07)
Attention deficit/ hyperactivity problems	54.1 (6.6)	54.3 (6.9)	−0.24 (−1.83 to 1.36)

Data are mean (SD).
*Mean difference with 95% CI was calculated using a t-test.
†Significant mean difference.
CBCL, Child Behavior Checklist; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

outcomes assessed at 2 years' CA. We studied this effect in the entire group of infants, and also examined any effect in the subgroups of infants who have subsequently developed severe BPD and NDI at 2 years' CA. The results of this study enable us to give neonatologists more insight into the effect of hydrocortisone on long-term behavioural problems in a population at high risk of these adverse outcomes.

In our study, we included infants with the highest risk for BPD who are therefore at a higher risk for adverse neurocognitive outcomes later in life.[25] Compared with an observational cohort study investigating behavioural problems in extremely preterm infants with BPD, we found similar elevated scores for mean total, internalising and externalising problem scales in both allocation groups.[3] Furthermore, almost 30% of the infants had behavioural disturbances already above the cut-off of 55, which has been shown indicative for serious disturbing behaviour problems that may increase later in life and thereby in need of intervention.[26] The high rates for almost all CBCL syndrome scales and DSM-IV-oriented subscales emphasise the need of early recognition and attention for behavioural problems of infants born very preterm as these problems often continue during childhood and young adulthood.[17]

Previous observational studies with systemic hydrocortisone in preterm infants at high risk of developing BPD reported no impaired brain growth or adverse neurodevelopmental outcome,[27] and retrospective studies on the comparison of hydrocortisone versus dexamethasone suggested less behavioural problems in infants treated with hydrocortisone.[11 28] In line with these studies, our placebo-controlled RCT showed no signs of harm of hydrocortisone treatment on behavioural outcomes and no difference in the combined outcome death or NDI at 2 years' CA, which strongly suggests that hydrocortisone does not lead to long-term adverse effects in preterm infants.

As mentioned earlier, the use of dexamethasone early in the first week of life is associated with long-term adverse neurodevelopmental outcome.[29] Furthermore, cohort studies investigating high-dose dexamethasone in the second week of life showed a

Table 3 Proportions of infants with critically elevated behavioural problems, T-score above 55, assessed by CBCL 1.5–5 years at 2 years' corrected age

	Multiple imputation analysis			
	Hydrocortisone n/total (%)	Placebo n/total (%)	Difference % (95% CI)*	OR (95% CI)†
CBCL				
Total problems	29/133 (21.8)	31/129 (24.6)	−2.3 (−13.6 to 9.0)	0.88 (0.46 to 1.67)
Internalising problems	23/133 (17.2)	27/129 (20.9)	−3.9 (−14.2 to 6.5)	0.78 (0.40 to 1.52)
Externalising problems	37/133 (27.8)	40/129 (31.0)	−3.5 (−15.8 to 8.9)	0.85 (0.47 to 1.54)
CBCL syndrome scales				
Emotionally reactive	21/133 (15.8)	25/129 (19.4)	−3.7 (−13.9 to 6.5)	0.77 (0.38 to 1.57)
Anxious/depressive	9/133 (6.8)	12/129 (9.3)	−2.5 (−9.9 to 4.9)	0.70 (0.25 to 1.96)
Somatic complaints	41/133 (30.8)	46/129 (35.7)	−4.6 (−17.9 to 8.8)	0.81 (0.44 to 1.49)
Withdrawn behaviour	51/133 (38.3)	53/129 (41.1)	−3.1 (−16.9 to 10.7)	0.88 (0.49 to 1.57)
Sleep problems	34/133 (25.6)	33/129 (25.6)	−0.1 (−11.9 to 11.6)	1.00 (0.53 to 1.85)
Attention problems	55/133 (41.4)	58/129 (45.0)	−3.1 (−17.1 to 10.8)	0.88 (0.50 to 1.56)
Aggressive behaviour	26/133 (19.5)	30/129 (23.3)	−4.3 (−15.5 to 6.9)	0.77 (0.40 to 1.51)
CBCL DSM-IV-oriented subscales				
Affective problems	44/133 (33.1)	45/129 (34.9)	−1.7 (−15.0 to 11.5)	0.93 (0.51 to 1.68)
Anxiety problems	13/133 (9.8)	22/129 (17.0)	−7.6 (−17.2 to 2.0)	0.50 (0.21 to 1.22)
Pervasive developmental	34/133 (25.6)	44/129 (34.1)	−8.7 (−21.3 to 3.8)	0.66 (0.36 to 1.21)
Oppositional defiant problems	30/133 (22.6)	28/129 (21.7)	1.3 (−10.3 to 12.9)	1.08 (0.55 to 2.14)
Attention deficit/hyperactivity problems	37/133 (27.8)	37/129 (28.7)	−0.6 (−13.5 to 12.3)	0.97 (0.51 to 1.84)

Data are percentages.
*Absolute risk difference was calculated using a generalised linear model using a binomial distribution with identity link.
†OR was calculated using a logistic regression model.
CBCL, Child Behavior Checklist; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

higher incidence of behavioural problems, especially on internalising behaviour, at school age.[9] A more recent observational cohort study in infants treated with low-dose dexamethasone in the second week of life showed higher proportions of infants in the abnormal range for behavioural problems.[10] These studies suggest that dexamethasone is associated with more behavioural problems later in life, while studies investigating hydrocortisone treatment report no increased risk for adverse behavioural outcomes. Although these findings suggest a different effect of dexamethasone and hydrocortisone on behavioural outcomes, an RCT comparing dexamethasone and hydrocortisone head to head is required to confirm or refute these findings.

For anxiety problems we found a statistically significant lower mean T-score in the hydrocortisone group. However, the mean difference with the placebo group was small and might be therefore of limited clinical relevance. Furthermore, in the complete case analysis we found a significant lower proportion of infants with pervasive developmental disorder and anxiety problems in the hydrocortisone group. These effects were no longer visible when multiple imputation was used to account for missing data. This is possibly due to the lower sample size in the complete case group and the higher probability of findings by chance, as we did not correct for multiple comparisons in our analyses.

Our previous published results of the SToP-BPD study showed high proportions of infants with BPD and NDI.[14 15] Both outcomes are considered independent risk factors for behavioural problems during childhood.[3 30] However, in our population we found no modifying effect of BPD or NDI on the effect of hydrocortisone treatment on behavioural outcome, suggesting that hydrocortisone treatment does not affect behavioural outcomes in subgroups of children with severe BPD or NDI.

Finally, the SToP-BPD study showed that hydrocortisone treatment is not associated with long-term NDI nor with behavioural problems at 2 years' CA. Future studies on long-term effects of postnatal steroids in preterm infants should include more 'subtle' mental health outcomes in early childhood in addition to the more standardised neurodevelopmental outcomes.

Our study has some limitations. Up to 30% of parents did not complete the CBCL 1½−5 and for some children the subscale scores were not registered. Infants with no CBCL data had different characteristics (multiple birth, parental education, multilingual environment) and outcomes (BPD, NDI) than infants with complete CBCL data. This may have led to an underestimation of rates of behavioural problems in cases with complete questionnaire data. Characteristics of infants within the database entered CBCL syndrome subscales and infants without were similar. In addition, more multiple births and higher level of parental education were reported in the hydrocortisone group which may have blurred the contrast between the two trial groups. However, the sensitivity analyses with cases with complete questionnaire data yielded similar results in both groups compared with the multiple imputation analyses. Also, data of the CBCL syndrome and DSM-IV-oriented subscales are highly skewed and not normally distributed. However, because of our sufficiently large sample size a t-test is also valid to analyse cases of non-normality.[31] With respect to the trial, a relatively high proportion of infants in the placebo group (53.5% (69/129)) were treated with open-label hydrocortisone, which may have diluted a possible effect of hydrocortisone on the behavioural outcomes. It remains unknown what the actual effect of the open-label treatment is on these current results, but meta-regression analyses of the dexamethasone RCTs investigating this modulating effect of open-label steroids on long-term outcomes showed no effect of open-label treatment.[32] Finally, observational studies have shown that the predictive value of a 2-year follow-up assessment for the true neurodevelopmental potential is limited, and assessment at the age of 5 years or later has better discriminating power for the general intellectual ability and behavioural problems.[33] In addition, assessment of behavioural problems depends on psychological well-being of

parents,[34] which may be still unstable shortly after preterm birth. Hence, follow-up of this study cohort at 5 years including neurodevelopmental and behavioural assessments is currently under way.

CONCLUSIONS

This randomised placebo-controlled clinical trial comparing systemic hydrocortisone initiated between 7 and 14 days after birth in ventilated very preterm infants to placebo treatment found high rates of behavioural problems at 2 years' CA; however, these were not associated with hydrocortisone treatment.

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Acknowledgements We would like to thank Marije Wolvers, statistical consultant, for her great advice on the statistical analyses.

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Funding This trial was funded by a project grant from the Netherlands Organisation for Health Research and Development (ZonMw) Priority Medicines for Children (11-32010-02).

Disclaimer The funding agency had no role in the design and conduct of the study; collection, management, analysis and interpretation of data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study protocol was approved by the Human Research Ethics Committee of the Academic Medical Center in Amsterdam, the Netherlands (reference number: 2010_297), and at each participating centre. Written informed consent was obtained from both parents before randomisation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Deidentified individual participant data (including data dictionaries) will be made available in addition to study protocol, the statistical analysis plan and the analytic code. The data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to CSHA-M, email: c.aarnoudse-moens@amsterdamumc.nl.

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