Short-term pulmonary and systemic effects of hydrocortisone initiated 7-14 days after birth in ventilated very preterm infants: a secondary analysis of a randomised controlled trial

Halbmeijer, N.M.; Onland, W.; Cools, F.; Kroon, A.; Heide-jalving, M. van der; Dijk, P.; ... ; SToP-BPD Study Grp

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Nienke M Halbmeijer ,[1,2] Wes Onland,[1,2] Filip Cools,[3] Andre Kroon,[4] Marja van der Heide-Jalving,[5] Peter Dijk,[6] Henrica L M van Straaten,[5] Arjan B te Pas,[7] Thilo Mohns,[8] Els Bruneel,[9] Arno F J van Heijst,[10] Boris Kramer,[11] Anne Debeer,[12] Inge A Zonnenberg,[13] Yoann Marechal,[14] Henry Blom,[15] Katleen Plaskie,[16] Maruschka P Merkus,[17] Martin Offringa ,[18] Anton H van Kaam,[1,2] SToP-BPD Study Group

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For numbered affiliations see end of article.

Correspondence to
Professor Anton H van Kaam, Neonatology, Amsterdam UMC Location University of Amsterdam, Meibergdreef 9 1105 AZ, Amsterdam, The Netherlands; a.h.vankaam@amsterdamumc.nl

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ABSTRACT

Objective Observational studies in preterm infants suggest that systemic hydrocortisone improves pulmonary condition but may also lead to systemic adverse effects. We report the short-term pulmonary and systemic effects of hydrocortisone initiated in the second week.

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 Data on extubation, ventilator settings, glucose levels, and blood pressure were recorded daily and analysed during the first 7 days of treatment using linear mixed-effects models.

Results Infants in the hydrocortisone group (24.3%) failed extubation less often compared with placebo (38.6%, crude risk difference: −14.3% (95% CI: −23.4% to −4.8%)). The estimated difference in daily rate of change between hydrocortisone and placebo was −0.42 cmH_2O (95% CI: −0.48 to −0.36) for mean airway pressure, −0.02 (95% CI: −0.02 to −0.01) for fraction of inspired oxygen, −0.37 (95% CI: −0.44 to −0.30) for respiratory index, 0.14 mmol/L (95% CI: 0.08 to 0.21) for blood glucose levels and 0.83 mm Hg (95% CI: 0.58 to 1.09) for mean blood pressure.

Conclusions Systemic hydrocortisone initiated between 7 and 14 days after birth in ventilated preterm infants improves pulmonary condition, thereby facilitating weaning and extubation from invasive ventilation. The effects of hydrocortisone on blood glucose levels and blood pressure were mild and of limited clinical relevance.

Trial registration number Netherlands Trial Register (NTR2768; https://www.trialregister.nl/trial/2640) and European Union Clinical Trials Register (EudraCT, 2010-023777-19).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Dexamethasone treatment in ventilator-dependent very preterm infants leads to a short-term improvement of lung function, and facilitates extubation, but also causes short-term adverse effects such as hyperglycaemia and hypertension.

⇒ Randomised data on short-term lung function changes and adverse systemic effects for hydrocortisone started after the first week are lacking.

WHAT THIS STUDY ADDS

⇒ This study shows that systemic hydrocortisone initiated between 7 and 14 days after birth in mechanically ventilated preterm infants improves pulmonary condition, and facilitates weaning and extubation.

⇒ Only mild elevations of blood glucose levels and blood pressure of hydrocortisone treatment were found in this study.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Clinicians can use this information to determine their weaning and extubation strategy.

INTRODUCTION

Mechanically ventilated preterm infants are at high risk of developing bronchopulmonary dysplasia (BPD).[1] Pulmonary inflammation plays an important role in its pathogenesis.[2] For this reason, ventilated preterm infants are often treated with postnatal corticosteroids to improve lung function, facilitate weaning and extubation, and reduce the risk of developing BPD.[3 4] Studies investigating the postnatal corticosteroid dexamethasone have shown positive effects on all these outcomes,[5–7] but its use is also associated with short-term (hyperglycaemia, hypertension) and long-term (neurodevelopmental) adverse effects.[3 4] Based on these concerns, the use of dexamethasone in preterm infants at risk of BPD

has dropped.[8] Hydrocortisone is increasingly used as an alternative, although evidence from randomised controlled trials (RCTs) showing its efficacy and safety when initiated after the first week of life is limited.[9]

The SToP-BPD (Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants) Study was the first large placebo-controlled RCT investigating the effect of systemic hydrocortisone treatment initiated in the second week of life in ventilator-dependent preterm infants. It showed that hydrocortisone does not reduce the risk of the combined outcome death or BPD at 36 weeks' postmenstrual age (PMA),[10] and is not associated with the combined outcome death or neurodevelopmental impairment at 2 years' corrected age.[11] Despite its lack of efficacy on BPD, clinicians may still decide to administer hydrocortisone to improve lung function and facilitate extubation. We previously reported that hydrocortisone reduces extubation failure compared with placebo, but it is unclear if this is mediated by an improvement in lung function over time. The same is true for the short-term adverse effect on hyperglycaemia and hypertension. Therefore, we performed a secondary in-depth analysis of the short-term pulmonary and systemic effects of hydrocortisone treatment compared with placebo as observed in the SToP-BPD Study.

METHODS

Study design and participants

This double-blind, placebo-controlled RCT was performed in 16 neonatal intensive care units in the Netherlands and Belgium between 15 November 2011 and 23 December 2016; details are published elsewhere.[10 12 13] In summary, infants born at a gestational age less than 30 weeks and/or with a birth weight less than 1250 g, who were ventilator dependent between day 7 and 14 of life, were randomly assigned to receive either hydrocortisone or placebo. Hydrocortisone sodium succinate was given to infants allocated to the intervention group in a tapered dosing scheme of 22 days with a cumulative dose of 72.5 mg/kg.

Study procedures and outcomes

Data on ventilator mode and settings were recorded at baseline and at the start of each day during the 22-day treatment course. Blood gas analyses, blood glucose levels and blood pressure measurements were performed as per local protocol and recorded if available for each day during the 22-day treatment course.

Outcomes of interest for this secondary analysis were the proportion of infants failing extubation and the median time to successful extubation. This analysis concerns an elaboration of our previously reported preliminary analysis of failure to extubate and duration of mechanical ventilation[10]; our previous analysis of failure to extubate was restricted to survivors at selected time points and currently a more strict definition of successful extubation is applied, that is, effectively remaining on non-invasive support for >72 hours.[14] Data on extubation were collected over the 22-day period of study treatment and infants who died during this period were considered to have failed extubation.[5] As daily lung function measurements were not feasible in this multicentre trial, we used the following indirect parameters of lung function: changes over time in mean airway pressure (MAWP) and respiratory index score (RI; defined as MAWP×FiO_2) in infants supported by mechanical ventilation, and in the total population the fraction of inspired oxygen (FiO_2) and partial pressure of carbon dioxide (pCO_2). In addition, we assessed changes over time in blood pressure (mean, systolic and diastolic) and blood glucose levels. The differences in rates of change in MAWP, FiO_2, RI, pCO_2, blood pressure and blood glucose levels were analysed during the first 7 days of treatment, as the hydrocortisone dosage was reduced after day 7 according to the tapered dosing scheme and the effect of hydrocortisone treatment on these outcomes is expected in the first days after start of treatment.

Statistical analysis

The sample size calculation for the trial was performed for the primary outcome death or BPD at 36 weeks' PMA, as previously reported.[10] Although we preplanned these secondary analyses, no formal sample size calculation was performed. Baseline infant characteristics are presented as mean and SD, or median and IQR for continuous variables, or counts and percentages for categorical variables where appropriate.

Data analyses were intention-to-treat with all patients included in their randomly assigned treatment group regardless of protocol deviations or use of open-label corticosteroids. A crude absolute risk difference was calculated between the proportions of infants failing extubation after the study treatment course of 22 days, and a time-to-event analysis was performed using Kaplan-Meier survival curves with a log-rank test for the 22-day study treatment course; time-to-event was calculated as the time between randomisation and successful extubation or the end of the 22-day study treatment course (censoring event, in case of failure of extubation).

Rates of change per day during the first 7 days of treatment for the MAWP, FiO_2, RI, pCO_2, blood glucose levels and blood pressure were compared between treatment groups with linear mixed-effects models including time (days), treatment group (placebo, hydrocortisone), treatment group×time interaction term, and adjusted for the stratification factor gestational age (<27 (reference group), ≥27 weeks) as fixed effects, and a random effect for the intercept. Maximum likelihood was used as the estimation method. Assumptions of linear mixed model analyses were checked using analysis of residuals. P values were calculated with the likelihood ratio test using the −2 log

Table 1 Baseline clinical characteristics

	Hydrocortisone (n=181)	Placebo (n=190)
Infant characteristics		
Gestational age, median (IQR), weeks	25.4 (24.9–26.4)	25.6 (24.7–26.4)
Birth weight, median (IQR), g	775 (643–865)	710 (629–810)
Male sex, no (%)	95 (52.5)	109 (57.4)
Small for gestational age, no (%)	26 (14.4)	38 (20.0)
Multiple birth, no (%)	70 (38.7)	54 (28.4)
Antenatal corticosteroids (any), no (%)	158 (87.3)	172 (90.5)
Ventilator settings at randomisation		
High-frequency oscillatory ventilation, no (%)	101 (55.8)	90 (47.4)
Mean airway pressure, mean (SD)	12.1 (2.3)	11.9 (2.2)
Fraction of inspired oxygen, median (IQR)	0.35 (0.30–0.45)	0.34 (0.29–0.40)
Respiratory index, median (IQR)*	4.3 (3.3–5.3)	3.9 (3.1–5.0)
Partial pressure of carbon dioxide, mean (SD), kPa	6.8 (1.3)	7.0 (1.3)
Other parameters at randomisation		
Mean blood pressure, mean (SD), mm Hg	39 (10)	38 (7)
Systolic blood pressure, mean (SD), mm Hg	52 (12)	52 (10)
Diastolic blood pressure, mean (SD), mm Hg	29 (9)	29 (8)
Blood glucose level, mean (SD), mmol/L	6.9 (2.3)	6.8 (2.5)

*Respiratory index was defined as mean airway pressure×fraction of inspired oxygen.
IQR, Interquartile range; SD, Standard deviation.

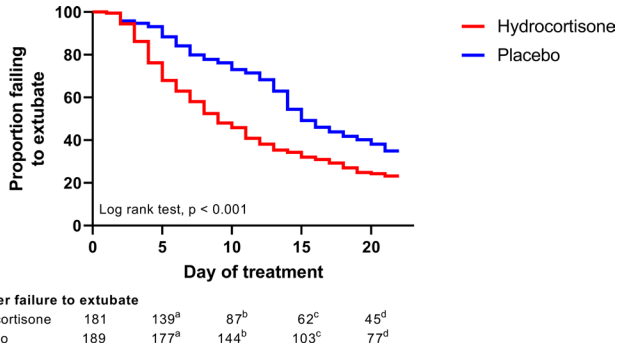

Figure 1 Kaplan-Meier analysis for proportion of infants failing to extubate over the full 22 days of treatment. [a]Includes nine deaths in the hydrocortisone group and eight deaths in the placebo group. [b]Includes four additional deaths in the hydrocortisone group and eight additional deaths in the placebo group. [c]Includes two additional deaths in the hydrocortisone group and six additional deaths in the placebo group. [d]Includes five additional deaths in the hydrocortisone group and three additional deaths in the placebo group.

likelihoods of the models with and without treatment group×-time interaction.

Sensitivity analyses were performed to check the robustness of the analyses excluding infants who received no study medication (n=3; 1 hydrocortisone, 2 placebo) and infants who received any open-label corticosteroids during the study treatment course (proportion failing extubation) and during the first 7 days of treatment (pulmonary and systemic effects). Also a sensitivity analysis was performed for the pulmonary and systemic effects over the first 7 days of treatment in survivors only as data on these outcomes are missing for deceased infants.

For all treatment effect estimators, 95% CIs are presented; all analyses were performed using two-sided tests; $p<0.05$ was regarded as statistically significant. No adjustments for multiple comparisons were made. Statistical analysis was performed in IBM SPSS Statistics for Windows, V.26.0 (IBM Corp).

RESULTS

In total, 372 infants were enrolled in the SToP-BPD Study of whom 182 infants were allocated to the hydrocortisone group and 190 infants to the placebo group; parents of one infant in the hydrocortisone group withdrew consent and this infant was excluded from all outcome analyses. Clinical characteristics at the time of randomisation were similar in both allocation groups, except for an average 65 g higher birth weight, a 0.4 higher RI score and 10% more multiple births in the hydrocortisone group (table 1).

In one infant in the placebo group, data on extubation were missing. At the end of the 22-day treatment course, a significantly lower proportion of hydrocortisone-treated infants failed extubation compared with the placebo group (24.3% vs 38.6%, respectively; crude risk difference: −14.3% (95% CI: −23.4% to −4.8%); log-rank test $p<0.001$; figure 1). For those infants successfully extubated after treatment initiation, the median time to extubation was 9 days (IQR: 5–19.5 days) in the hydrocortisone group and 15 days (IQR: 10–23 days) in the placebo group.

MAWP, FiO_2 and RI decreased significantly over the first 7 days of treatment in the hydrocortisone group compared with the placebo group with an estimated difference in rates

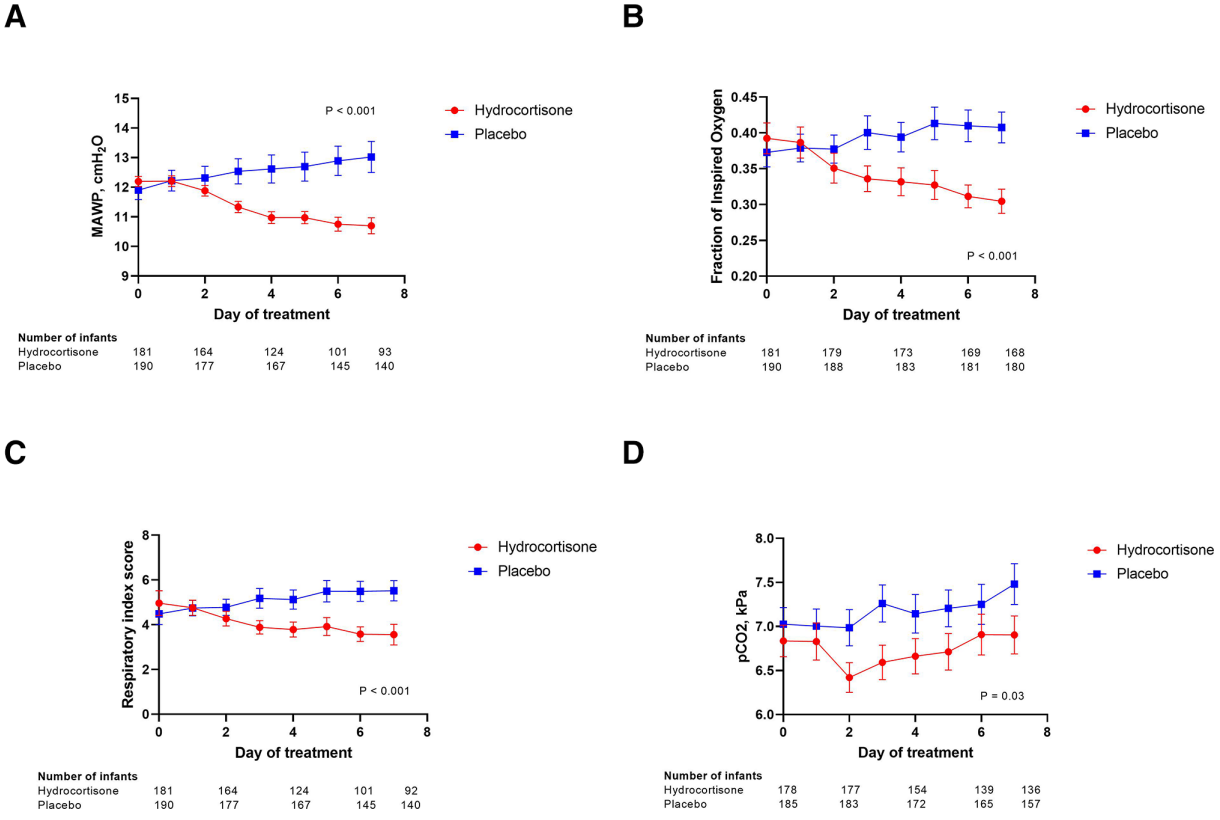

Figure 2 (A) Observed mean airway pressure (MAWP), (B) fraction of inspired oxygen, (C) respiratory index score and (D) partial pressure of carbon dioxide (pCO_2) during the first 7 days of treatment (observed mean daily values with 95% CIs).[a] [a]P values shown for the likelihood ratio test calculated using the −2 log likelihoods of the mixed models with and without treatment group×time interaction.

Table 2 Differences in change over time in pulmonary and systemic outcomes between hydrocortisone and placebo group in the intention-to-treat population, during the first 7 days of treatment*

Outcomes	Estimated difference in rate of change per day (95% CI)†, hydrocortisone vs placebo	P value‡
Mean airway pressure (cmH_2O)§	−0.42 (−0.48 to −0.36)	<0.001
FiO_2	−0.02 (−0.02 to −0.01)	<0.001
Respiratory index score	−0.37 (−0.44 to −0.30)	<0.001
pCO_2 (kPa)¶	−0.04 (−0.08 to −0.003)	0.03
Blood glucose level (mmol/L)¶	0.14 (0.08 to 0.21)	<0.001
Mean blood pressure (mm Hg)	0.83 (0.58 to 1.09)	<0.001
Systolic blood pressure (mm Hg)	1.00 (0.70 to 1.31)	<0.001
Diastolic blood pressure (mm Hg)	0.86 (0.60 to 1.12)	<0.001

*Linear mixed models including time (days), treatment group (placebo, hydrocortisone), treatment group×time interaction and the stratification factor gestational age (<27, ≥27 weeks) as fixed factors. Reference groups are <27 weeks for gestational age and placebo for treatment group. Dependency of repeated measures was taken into account by including a random intercept for each patient and maximum likelihood was used as the estimation method.
†Estimated difference in linear rate of change per day (ie, difference in mean change in outcome variable per day), estimated by the regression coefficient of the treatment group×time interaction.
‡P values shown for the likelihood ratio test calculated using the −2 log likelihoods of the maximum likelihood mixed models with and without treatment group×time interaction.
§For infants supported with conventional mechanical ventilation and without a recorded mean airway pressure (MAWP), the MAWP was calculated using the following formula: $[MAWP=(PIP–PEEP)\times T_i/(T_i+T_e)+PEEP]$.[26] In this formula, PIP is the peak inspiratory pressure, PEEP is positive end-expiratory pressure, T_i is inspiratory time and T_e is expiratory time.
¶The units used for the collected blood glucose levels and pCO_2 values differ per centre, mg/dL or mmol/L for blood glucose level and mm Hg or kPa for pCO_2. To compare the blood glucose levels and pCO_2 values in the total population, the available blood glucose levels in mg/dL were converted to mmol/L and for the pCO_2 mm Hg was converted to kPa.
FiO_2, fraction of inspired oxygen; pCO_2, partial pressure of carbon dioxide.

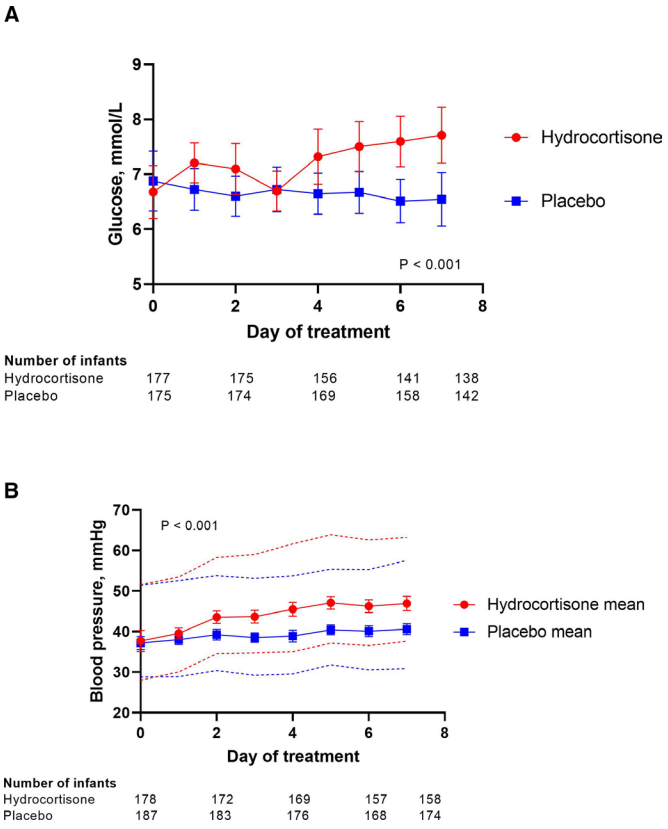

Figure 3 (A) Observed blood glucose levels and (B) blood pressure during the first 7 days of treatment (observed mean daily values with 95% CIs). For blood pressure, the upper dotted line represents the systolic blood pressure and the lower dotted line the diastolic blood pressure.[a] [a]P values shown for the likelihood ratio test calculated using the −2 log likelihoods of the mixed models with and without treatment group×time interaction.

of change between the hydrocortisone and placebo group of −0.42 cmH_2O (95% CI: −0.48 to −0.36) per day for MAWP (p<0.001), −0.02 (95% CI: −0.02 to −0.01) per day for FiO_2 (p<0.001) and −0.37 (95% CI: −0.44 to −0.30) per day for RI (p<0.001) (figure 2A–C and table 2). Availability of blood gas analyses ranged from 98% of infants at the start of study treatment to 79% of infants on day 7 of treatment. A significant difference in daily rate of change was seen for the pCO_2 in the hydrocortisone-treated infants compared with the placebo group (estimated difference in rate of change: −0.04 kPa (95% CI: −0.08 to −0.003) per day; p=0.03; figure 2D and table 2).

The rate of change in blood glucose level of the hydrocortisone-treated infants was significantly higher compared with the placebo group (estimated difference in rate of change: 0.14 mmol/L (95% CI: 0.08 to 0.21) per day; p<0.001; figure 3A and table 2). In addition, during the first 7 days of treatment, the mean, systolic and diastolic blood pressure increased significantly more in the hydrocortisone group compared with the placebo group (estimated difference in rate of change: 0.83 mm Hg (95% CI: 0.58 to 1.09), 1.00 mm Hg (95% CI: 0.70 to 1.31), 0.86 mm Hg (95% CI: 0.60 to 1.12) per day, respectively; p<0.001; figure 3B and table 2).

Sensitivity analyses in the surviving infants only and excluding infants who received no study medication or open-label corticosteroids yielded similar results (online supplemental figure 1, tables 1 and 2, online supplemental file 2).

DISCUSSION

This study shows that systemic hydrocortisone initiated between 7 and 14 days after birth in mechanically ventilated preterm infants born before 30 weeks' gestation improves lung function, assessed by the MAWP and oxygen need, and facilitates extubation. Furthermore, hydrocortisone treatment is associated with a higher daily rate of change in blood glucose level and more increase in blood pressures during the first 7 days of treatment.

The effect of hydrocortisone as compared with placebo on the course in lung function during the first 7 days of study treatment was estimated by the between-groups difference in daily rate of change in MAWP, FiO_2 and RI. Although the estimated beneficial effect of hydrocortisone on rate of change in MAWP and FiO2 per day may appear modest, over a time period of a number of days it accumulates to a clinically relevant improvement, resulting in a higher rate of successful extubation and shorter time to extubation. Importantly, the faster weaning of ventilatory pressures in the hydrocortisone group compared with the placebo group was not accompanied by a clinically relevant difference in the course in pCO_2 between both groups. In addition, our study showed that the median time to extubation was 9 days in hydrocortisone-treated infants compared with 15 days in the placebo group. In line with recently published population-based observational studies, this reduction in the duration of mechanical ventilation did not result in a decrease of BPD incidence.[15 16] However, shortening invasive ventilation by 6 days may have important implications as retrospective cohort studies

have shown that each additional day of mechanical ventilation was negatively correlated with long-term neurodevelopmental impairment.[17 18]

RCTs investigating prophylactic hydrocortisone treatment, started in the first week of life, to date, have not reported the impact on lung function parameters such as MAWP, FiO_2 and RI.[19–23] The PREMILOC Study, investigating early low-dose hydrocortisone in preterm infants, reported a higher rate of extubated infants by day 7 of treatment in the hydrocortisone group (58%) compared with the placebo group (47%).[19] This finding indirectly suggests that, in line with our study, prophylactic hydrocortisone also improves the pulmonary condition of these infants. However, comparison of these results with the current report should be done cautiously. In the early and prophylactic studies, hydrocortisone is started shortly after birth when ventilator-induced lung injury is still limited. In contrast, infants included in our study in the second week of life were at a higher risk of having a poorer pulmonary condition at the start of hydrocortisone treatment.

For the mostly investigated corticosteroid dexamethasone, several RCTs showed short-term lung function improvement as reflected by lower ventilator settings 48 hours after start of treatment and faster extubation.[3 4 6 7 24] Our findings are in line with these studies, which strongly suggests that both dexamethasone and hydrocortisone have beneficial effects on short-term lung function in mechanically ventilated preterm infants. Since there are no RCTs comparing head-to-head hydrocortisone versus dexamethasone, it remains unknown which drug is superior in achieving these rapid improvements in pulmonary condition.

Other systemic outcome parameters, such as blood pressure and glucose levels, are also affected by corticosteroids. We found a significantly increase of blood glucose levels and blood pressure per day in hydrocortisone-treated infants. In this patient population at risk of hyperglycaemia, the observed higher glucose levels were in most cases relatively mild, as previously reported.[10] The rate of hypertension, using predefined cut-off values depending on gestational age, was low and similar in both groups.[10] Studies on prophylactic hydrocortisone and studies on prophylactic and targeted dexamethasone treatment showed a similar increase in blood glucose levels and blood pressure over time,[5 25] and reported a significant increased risk for both hyperglycaemia and hypertension.[3 4]

The primary goal of systemic corticosteroid treatment is to reduce the incidence of BPD at 36 weeks' PMA, and our previous report showed that hydrocortisone was not effective in reducing this outcome.[10] However, corticosteroids are also administered to facilitate weaning and extubation from (protracted) invasive mechanical ventilation. Therefore, the results of this secondary analysis of the SToP-BPD Study have important clinical implications. This study shows that hydrocortisone will improve the pulmonary condition facilitating earlier weaning of MAWP and FiO_2. Furthermore, this pulmonary improvement leads to successful extubation in most infants at a median time point of 9 days. The relatively mild elevations of blood glucose levels and blood pressure do not seem to outweigh these beneficial effects on short-term lung function. Clinicians can use this information to determine their weaning and extubation strategy.

Limitations

Our study has a few limitations. First, after extubation, infants were supported by non-invasive respiratory support, and invasive MAWP was no longer measured. However, as the median time to successful extubation was 9 days in the hydrocortisone group, we do not expect that this limitation has hampered our findings on the MAWP and RI. Second, a relatively high proportion of infants in the placebo group (56.8%) was eventually treated with open-label hydrocortisone, which may have diluted a possible effect of hydrocortisone on the ventilator and oxygen requirements. The performed sensitivity analysis to explore possible bias by open-label corticosteroids seems reassuring as it yielded similar treatment effect for any of the outcome variables.

CONCLUSION

Systemic hydrocortisone initiated between 7 and 14 days after birth in mechanically ventilated preterm infants born before 30 weeks' gestation significantly improves the pulmonary condition, thereby facilitating weaning and extubation from invasive mechanical ventilation. The effects of hydrocortisone on blood glucose levels and blood pressure were mild and of limited clinical relevance.

Author affiliations
[1]Neonatology, Amsterdam UMC Location University of Amsterdam, Amsterdam, The Netherlands
[2]Research Institute, Amsterdam Reproduction and Development, Amsterdam, The Netherlands
[3]Neonatology, Universitair Ziekenhuis Brussel, Brussels, Belgium
[4]Neonatology, Erasmus Medical Center, Rotterdam, The Netherlands
[5]Neonatology, Isala Medical Center, Zwolle, The Netherlands
[6]Neonatology, University Medical Centre Groningen, Beatrix Children's Hospital, Groningen, The Netherlands
[7]Neonatology, Leiden University Medical Center, Leiden, The Netherlands
[8]Neonatology, Maxima Medical Centre Location Veldhoven, Veldhoven, The Netherlands
[9]Neonatology, Ziekenhuis Oost-Limburg, Genk, Belgium
[10]Neonatology, Radboud University Medical Center-Amalia Children's Hospital, Nijmegen, The Netherlands
[11]Neonatology, Maastricht University Medical Center+, Maastricht, The Netherlands
[12]Neonatology, Universitair Ziekenhuis Leuven, Leuven, Belgium
[13]Neonatology, University Medical Center Utrecht, Utrecht, The Netherlands
[14]Neonatology, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium
[15]Neonatology, Universitair Ziekenhuis Antwerpen, Edegem, Belgium
[16]Neonatology, St Augustinus Ziekenhuis, Antwerp, Belgium
[17]Epidemiology and Data Science, Amsterdam UMC Location University of Amsterdam, Amsterdam, The Netherlands
[18]Neonatology and Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Ontario, Canada

Twitter Arjan B te Pas @None

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Collaborators SToP-BPD Study Group members: Debbie H Nuytemans, Moniek van de Loo (Department of Neonatology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands), Inez Vereeck (Department of Neonatology, Universitair Ziekenhuis Brussel, Brussels, Belgium), Renate Swarte (Department of Neonatology, Sophia Children's Hospital, Erasmus MC, Rotterdam, The Netherlands), Karin Rademaker (Department of Neonatology, University Medical Center, Utrecht, The Netherlands), Ellen de Kort (Department of Neonatology, Maxima Medical Center Veldhoven, The Netherlands), Eric Cavartorta, Anne Rassart (Department of Neonatology, Centre Hospitalier Universitaire Marie Curie, Charleroi, Belgium), An Eerdekens (Department of Neonatology, Universitair Ziekenhuis Leuven, Leuven, Belgium), Margriet Stuijvenberg (Department of Neonatology, University Medical Center Groningen, Beatrix Children's Hospital, University of Groningen, Groningen, The Netherlands), René Matthijsse, Willem de Boode (Department of Neonatology, Radboud University Medical Center-Amalia Children's Hospital, Nijmegen, The Netherlands), Hendrik Niemarkt, Ilse van Hattum (Department of Neonatology, Medical University Center Maastricht, Maastricht, The Netherlands), Liesbeth Groot Jebbink, Susanne M Mulder-de Tollenaer (Department of Neonatology, Isala Medical Center, Zwolle, The Netherlands), Ratna Tan (Department of Neonatology, Leiden University Medical Center, Leiden, The Netherlands), Claire Theyskens (Department of Neonatology, Ziekenhuis Oost-Limburg, Genk, Belgium), Mirjam van Weissenbruch (Department of Neonatology, Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands), Elke Dierckx (St Augustinus Ziekenhuis, Antwerp, Belgium). All members contributed to

the design of the study protocol, data collection, data reporting and revision of the first draft of the manuscript. They received no compensation for their contributions.

Contributors FC, AK, MvdH-J, PD, HLMvS, ABtP, TM, EB, AFJvH, BK, AD, IAZ, YM, HB, KP and MO are local investigators at the participating centres, and made substantial contributions to the concept and design of the study, and interpretation of data. NMH performed the statistical analyses, prepared the data tables, drafted the initial manuscript and revised the manuscript. MPM made substantial contributions to the interpretation of data, and reviewed and revised the manuscript. WO and AHvK are local investigators, made substantial contributions to the concept and design of the study, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. AHvK accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

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Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Ethics Committee of the Academic Medical Center in Amsterdam, the Netherlands (reference number: 2010_297) and the local Ethics Committee of each participating hospital. Written informed consent was obtained from both parents before randomisation.

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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 analytical 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 Professor Anton van Kaam (email: a.h.vankaam@amsterdamumc.nl).

ORCID iDs
Nienke M Halbmeijer http://orcid.org/0000-0002-6588-2265
Martin Offringa http://orcid.org/0000-0002-4402-5299

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