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ABSTRACT

Objective To explore clinical effect modifiers of systemic hydrocortisone in ventilated very preterm infants for survival and neurodevelopmental outcome at 2 years' corrected age (CA).

Design Secondary analysis of a randomised placebo-controlled trial.

Setting Dutch and Belgian neonatal intensive care units.

Patients Infants born <30 weeks' gestational age (GA), ventilator-dependent in the second week of postnatal life.

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

Main outcome measures The composite of death or neurodevelopmental impairment (NDI) at 2 years' CA and its components. Candidate effect modifiers (GA, small for GA, respiratory index, sex, multiple births, risk of moderate/severe bronchopulmonary dysplasia or death) were analysed using regression models with interaction terms and subpopulation treatment effect pattern plots.

Results The composite outcome was available in 356 (96.0%) of 371 patients (one consent withdrawn). For this outcome, treatment effect heterogeneity was seen across GA subgroups (<27 weeks: hydrocortisone (n=141) vs placebo (n=156), 54.6% vs 66.2%; OR 0.61 (95% CI 0.38 to 0.98); ≥27 weeks: hydrocortisone (n=30) vs placebo (n=31), 66.7% vs 45.2%; OR 2.43 (95% CI 0.86 to 6.85); p=0.02 for interaction). This effect was also found for the component death (<27 weeks: 20.1% vs 32.1%; OR 0.53 (95% CI 0.32 to 0.90); ≥27 weeks: 28.1% vs 16.1%; OR 2.04 (95% CI 0.60 to 6.95); p=0.049 for interaction) but not for the component NDI. No differential treatment effects were observed across other subgroups.

Conclusion This secondary analysis suggests that in infants <27 weeks' GA, systemic hydrocortisone may improve the outcome death or NDI, mainly driven by its

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The SToP-BPD (Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants) Study showed no difference in the primary composite outcome death or bronchopulmonary dysplasia and long-term composite outcome death or neurodevelopmental impairment (NDI) at 2 years' corrected age between both allocation groups in the total study population of infants born <30 weeks' gestation or with a birth weight <1250 g.

⇒ Previous subgroup analysis of the SToP-BPD Study at 36 weeks' postmenstrual age suggested a reduced death rate in favour of hydrocortisone in the gestational age subgroup below 27 weeks.

⇒ Identifying factors that modify hydrocortisone treatment effect is important as it will allow selection of subsets of patients with a potential better or worse benefit–harm balance.

WHAT THIS STUDY ADDS

⇒ This secondary analysis of the SToP-BPD trial suggests a potential beneficial systemic hydrocortisone treatment effect in the subgroup of ventilated preterm infants born before 27 weeks' gestation on the long-term composite outcome death or NDI, mainly driven by its component death.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study provide further guidance for larger future clinical trials on postnatal corticosteroids to prevent bronchopulmonary dysplasia in patients with certain risk factors.

component death. There was insufficient evidence for other selected candidate effect modifiers.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) remains the most common morbidity of extreme prematurity.[1 2] Its pathogenesis is multifactorial, but pulmonary inflammation is considered an important risk factor.[3] Because of their anti-inflammatory effects, corticosteroids have been studied for the prevention and treatment of BPD.[4 5] The corticosteroid dexamethasone reduces the risk of BPD,[4] but has also been associated with an increased incidence of neurodevelopmental impairment (NDI).[6–8] The SToP-BPD (Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants) Study investigated if systemic hydrocortisone, started in the second week after birth in ventilator-dependent very preterm infants, would be an effective and safe alternative. It showed that hydrocortisone did not reduce the risk of death or BPD at 36 weeks' postmenstrual age (PMA),[9] and did not increase the risk of death or NDI at 2 years' corrected age (CA).[10]

The estimated overall treatment effect of the SToP-BPD Study reflects the average effect for the total study population. Yet, it is conceivable that infants with different characteristics may respond differently to the same intervention. Identifying factors that modify hydrocortisone treatment effect is important as it will allow selection of subsets of patients with a potential better or worse benefit–harm balance. Previous subgroup analysis of the SToP-BPD Study at 36 weeks' PMA for preselected patient characteristics suggested a differential treatment effect for the primary outcome component death across gestational age (GA) subgroups.[9] This illustrates that the treatment effect of hydrocortisone may vary across subpopulations of infants. It is unclear if effect modification also applies to the long-term outcome. Therefore, the objective of the current study was to explore potential clinical effect modifiers of hydrocortisone treatment on long-term survival and neurodevelopmental outcome at 2 years' CA of infants included in the SToP-BPD Study.

METHODS

Study population

The SToP-BPD Study is a double-blind, placebo-controlled, randomised trial, which was performed between November 2011 and December 2016 in 16 neonatal intensive care units in the Netherlands and Belgium.[9 11] It included infants born with a GA less than 30 weeks and/or with a birth weight below 1250 g who were ventilator dependent in the second week of life. Infants were randomly assigned to receive either a 22-day course of systemic hydrocortisone (cumulative dose 72.5 mg/kg) or placebo.

Key long-term composite outcome and its individual components

Follow-up assessment at 2 years' CA was performed between April 2014 and June 2019. The key long-term outcome concerned the composite of death or NDI at 2 years' CA and its individual components. The estimated overall treatment effect on these outcomes was published previously.[10] NDI 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; cerebral palsy greater than level II on the Gross Motor Function Classification System; hearing or visual impairment. More details on definitions can be found in the online supplemental file 2.

Candidate treatment effect modifiers

Candidate treatment effect modifiers included the preselected risk factors GA, small for GA (SGA) (<10th percentile Fenton growth chart), respiratory index (mean airway pressure×fraction of inspired oxygen (FiO_2)) at randomisation, sex and multiple pregnancies (online supplemental file 2).[12] Information on the preselected risk factors parental education and multilingual environment was missing for the deceased infants; therefore, these were not included. The included candidate treatment effect modifiers are postulated, biologically plausible risk factors for BPD and death.[11 13] BPD is considered an important modifier of long-term outcome and is associated with neurodevelopmental delay.[14]

To evaluate whether the a priori risk of BPD would modulate the effect of hydrocortisone on survival and neurodevelopmental outcome, the Neonatal BPD Outcome Estimator, developed by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network was post hoc selected as a candidate effect modifier.[15] This composite risk score considers the simultaneous impact of GA, birth weight, race/ethnicity, sex, respiratory support and FiO_2 on the outcome death or BPD. Combination of individual risk factors in a composite risk score predicts more accurately the underlying individual infants' BPD risk and facilitates analysis across different risk distributions.[16] Since we had only access to the equation for postnatal day 1 and day 3, we used the model at postnatal day 3 and the respiratory settings at randomisation to calculate the individual predicted probability of moderate/severe BPD or death of each individual infant.

Statistical analysis

Data analyses were performed in the intention-to-treat population, including all randomised patients regardless of protocol deviations or use of open-label corticosteroids. Subgroups were categorised using prespecified cut-off points: GA groups (<27, ≥27 weeks), SGA (yes, no), respiratory index (≤median, >median of the total study population), sex (male, female) and multiple pregnancies (multiple births, singleton).[12] Crude relative and absolute treatment effect estimates within subgroups were calculated with the corresponding 95% CI. Treatment effect heterogeneity across subgroups was statistically tested through the corresponding (treatment×subgroup) interaction effect in a logistic regression model and generalised linear model including treatment, subgroup and (treatment×subgroup) interaction term (online supplemental file 3).[12] Within-subgroup treatment effects are estimated independent of whether the test of the specific interaction term is statistically significant.

Since dichotomising continuous variables may obscure important information that is contained across the full continuum of values, we explored post hoc treatment effect heterogeneity according to the candidate effect modifiers across their full spectrum of values, using subpopulation treatment effect pattern plots (STEPP).[17] STEPP is a non-parametric, graphical approach which constructs overlapping patient subpopulations along the continuum of the covariate, that is, a 'sliding-window' pattern of subpopulations. STEPP analysis improves the precision of the estimated treatment effects within the subgroups by plotting treatment effect estimates against the median values of the specific covariate in the subpopulations to provide a graphical presentation of the heterogeneity of treatment effects. STEPP

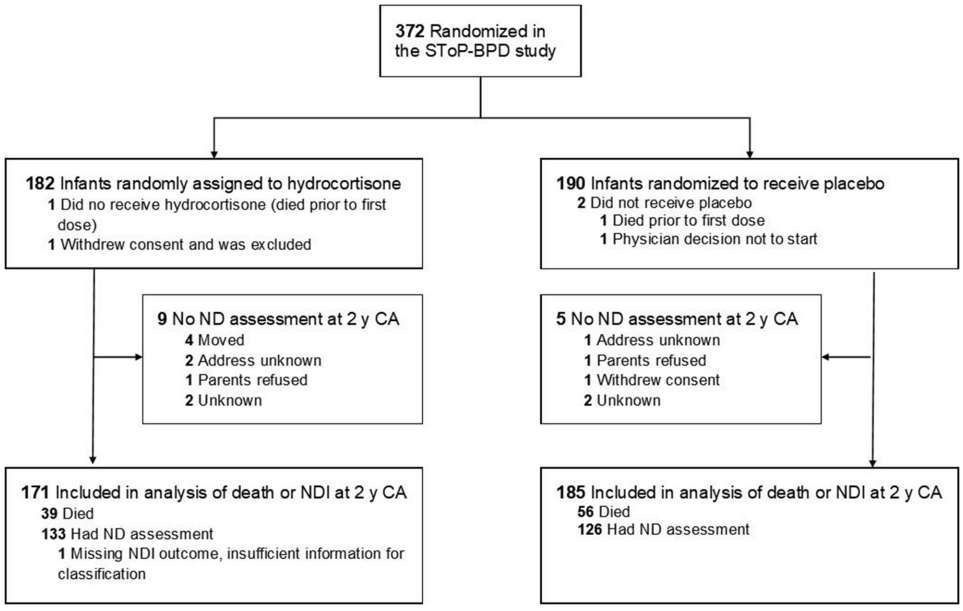

Figure 1 Consolidated Standards of Reporting Trials flow diagram. CA, corrected age; ND=neurodevelopmental; NDI, neurodevelopmental impairment; SToP-BPD, Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants.

makes no prior assumptions regarding the pattern of interaction and thus has the potential to highlight complex associations.[18] The STEPP analyses were performed according to the general guidelines as described by Yip *et al*.[17] Subpopulations were chosen using two window smoothing parameters r2 and r1, that is, a sample size of 100 infants per subset (r2) and an overlap of 50 infants (r1) between subsequent subsets, to create a minimum of four to five subgroups with 50% overlap. For a formal interaction test, the p value for interaction from a supremum test statistic is reported. To assess the consistency of the results, sensitivity analyses with varying sample size (r2) and varying overlap (r1) were performed.

All analyses were performed using two-sided tests and $p<0.05$ was regarded as statistically significant; as the analyses were hypothesis generating only, we did not adjust for multiple testing. Statistical analysis was performed in SPSS Statistics for Windows, V.28.0 (IBM Corp), R V.4.1.3 for Windows (R-package stepp and lattice; R Foundation for Statistical Computing) and RStudio.

RESULTS

The composite outcome death or NDI at 2 years' CA was available in 356 (96.0%) of 371 infants; 95 infants died before 2 years' follow-up, and neurodevelopment assessment was performed in 262 infants (one infant had a missing NDI outcome) (figure 1). Baseline characteristics of both treatment groups were similar, except for more multiple births in the hydrocortisone group (table 1).

Subgroup analyses showed a differential treatment effect across the dichotomised GA subgroups for the composite outcome of death or NDI at 2 years' CA, with a reduced rate in infants born before 27 weeks' gestation in the hydrocortisone group compared with the placebo group (<27 weeks: hydrocortisone (n=141) vs placebo (n=156), 54.6% vs 66.2%, crude absolute risk difference (ARD) −11.6% (95% CI −22.4% to −0.5%), crude OR 0.61 (95% CI 0.38 to 0.98); and ≥27 weeks: hydrocortisone (n=30) vs placebo (n=31), 66.7% vs 45.2%, crude ARD 21.5% (95% CI −3.2% to 42.8%), crude OR 2.43 (95% CI 0.86 to 6.85); p=0.02 for interaction tests) (figure 2A and online supplemental tables S1 and S2). This was also found for the component death (hydrocortisone vs placebo: <27 weeks, 20.1% vs 32.1%, crude ARD −11.9% (95% CI −21.4% to −2.1%); ≥27 weeks, 28.1% vs 16.1%; crude ARD 12.0% (95% CI −8.8% to 31.5%), p=0.04 for interaction test; crude OR <27 weeks, 0.53 (95% CI 0.32 to 0.90); crude OR ≥27 weeks, 2.04 (95% CI 0.60 to 6.95), p=0.049 for interaction test), but not for the NDI component (figure 2B,C and online supplemental tables S1 and S2). No differential treatment effects were observed across the subgroups of other preselected categorical candidate effect modifiers (figure 2A–C and online supplemental tables S1 and S2).

In line with the dichotomised GA subgroup analysis, STEPP suggested treatment effect heterogeneity for the composite outcome death or NDI and its component death, with benefit of

Table 1 Clinical characteristics at birth and at randomisation of infants with a composite outcome death or neurodevelopmental impairment at 2 years' corrected age

	Hydrocortisone (n=171)	Placebo (n=185)
Infant characteristics		
Gestational age, median (IQR), weeks	25.4 (24.9–26.4)	25.6 (24.7–26.4)
Birth weight, median (IQR), g	777 (640–865)	710 (628–810)
Male sex, n (%)	89 (52.0)	105 (56.8)
Small for gestational age, n (%)*	24 (14.0)	37 (20.0)
Multiple births, n (%)	66 (38.6)	51 (27.6)
Respiratory settings at randomisation		
High-frequency oscillatory ventilation, n (%)	95 (55.6)	86 (46.5)
Fraction of inspired oxygen, median (IQR)	0.35 (0.30–0.45)	0.34 (0.29–0.40)
Respiratory index, median (IQR)†	4.3 (3.3–5.4)	3.9 (3.1–5.0)
Predicted probability of moderate/severe BPD or death, median (IQR), %‡	88.7 (83.1–93.0)	90.2 (85.1–93.4)

*Small for gestational age was defined as birth weight less than the 10th percentile on the Fenton growth chart.
†Respiratory index was defined as mean airway pressure×fraction of inspired oxygen.
‡Predicted probability of moderate/severe BPD was calculated using the NICHD Neonatal BPD Outcome Estimator.
BPD, bronchopulmonary dysplasia; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

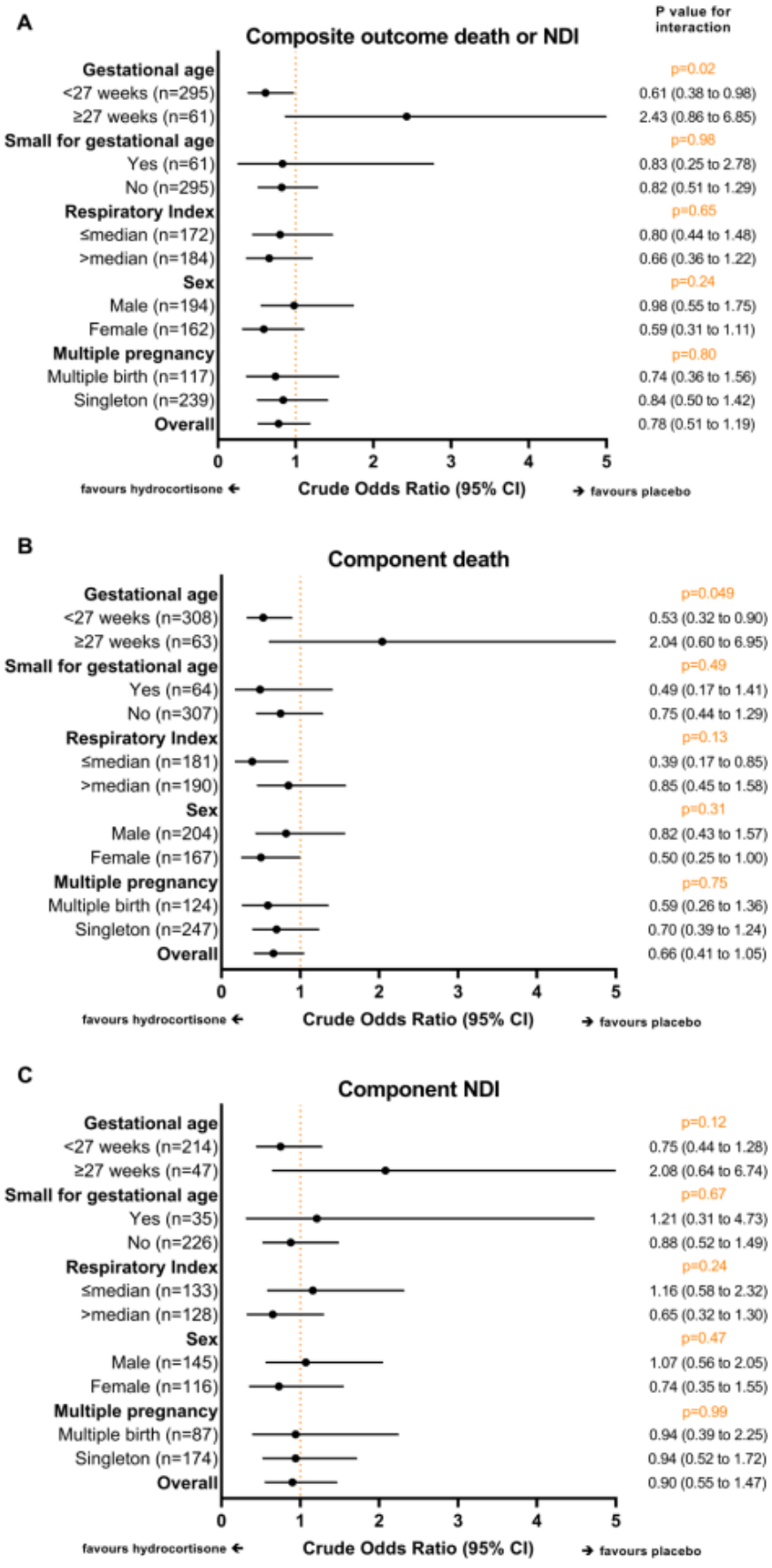

Figure 2 Forest plot of the subgroup analyses of the composite outcome death or neurodevelopmental impairment (NDI) at 2 years' corrected age (A) and its individual components (B,C) at 2 years' corrected age.[a] [a]Subgroup analyses were performed and statistically tested with interaction effect of the specific subgroup and treatment in logistic regression models. P value for interaction is reported.

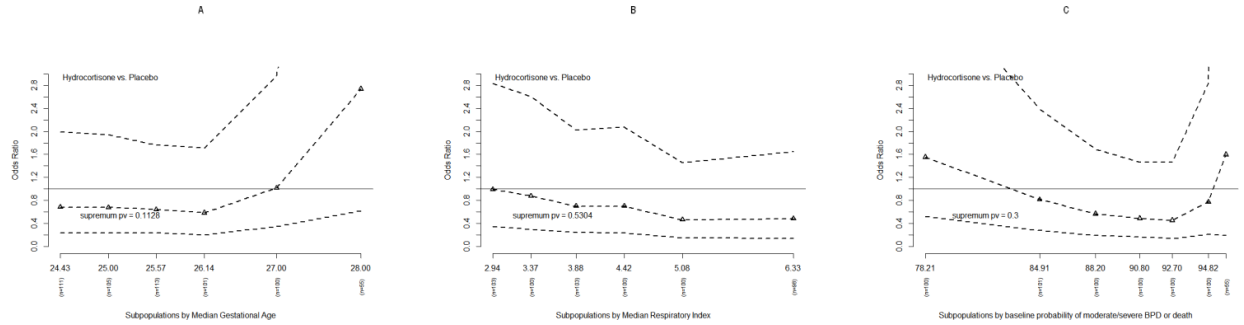

Figure 3 STEPP of the heterogeneity of hydrocortisone versus placebo treatment effect by gestational age (A), respiratory index (B) and predicted probability of moderate/severe BPD or death (C) on the long-term outcome death or neurodevelopmental impairment at 2 years' corrected age, based on crude OR estimates.[a] [a]Subpopulations were chosen with sample size r2 of 100 infants per subset and overlap r1 of 50 infants between subsequent subsets. Shown are pointwise estimates and 95% CIs of the OR per subpopulation, plotted at the median value of the corresponding subpopulation. Interaction p values derived from permutation tests with 2500 resampling steps. An OR <1 indicates that hydrocortisone is the preferred strategy. BPD, bronchopulmonary dysplasia; STEPP, subpopulation treatment effect pattern plots.

hydrocortisone treatment across the GA range below 27 weeks, although this did not yield statistical significance (figure 3A and online supplemental figures 1A and 2A). Exploration of patterns of treatment effects for varying levels of respiratory index and probability of moderate/severe BPD or death following the NICHD Neonatal BPD Outcome Estimator suggested no clear treatment heterogeneity across subpopulations for the composite outcome and its individual components (figure 3B,C and online supplemental figures 2 and 3). Sensitivity STEPP analyses yielded results (online supplemental table 3).

DISCUSSION

This prespecified secondary analysis of the SToP-BPD trial is to our knowledge the first study exploring potential clinical effect modifiers of hydrocortisone treatment initiated in the second week after birth in ventilated very preterm infants for long-term survival and neurodevelopmental outcome. We observed a modifying treatment effect of GA; infants born before 27 weeks' gestation had a significantly reduced rate of the composite outcome death or NDI at 2 years' CA in favour of hydrocortisone, mainly driven by a reduction in death. No other selected candidate treatment effect modifiers showed sufficient evidence of a differential hydrocortisone treatment effect.

Lower GA is an important risk factor for neonatal morbidities, including an inverse relation with impaired neurodevelopmental outcome.[19 20] Consequently, it is conceivable that the most immature infants may have a different risk profile than more mature infants and may respond differently to hydrocortisone treatment. An exploratory analysis of the PREMILOC Study, a randomised trial involving prophylactic hydrocortisone treatment, suggested a differential hydrocortisone effect in GA subgroups for neurodevelopmental outcome. The authors reported a significant improvement in neurodevelopmental outcomes following hydrocortisone treatment in the subgroup of infants born at 24–25 weeks' gestation, which was not the case in the subgroup of infants born at 26–27 weeks' gestation.[21] This improvement in neurodevelopment in the specific subgroup of infants born at 24–25 weeks of gestation was not observed in our STEPP for GA. Important differences between the two studies in patient characteristics, dosage and timing of hydrocortisone treatment may explain this discrepancy.

In the initial SToP-BPD Study, subgroup analyses were performed for the primary outcome death or BPD at 36 weeks' PMA and its components.[9] Across categorical GA subgroups (<27 or ≥27 weeks), a differential treatment effect was found for the component death, with a reduced rate in favour of hydrocortisone in the GA subgroup below 27 weeks. Consistent with this earlier finding at 36 weeks' PMA, the current study also observed a statistically significant and clinically relevant reduction in mortality at 2 years' CA in favour of hydrocortisone in infants born below 27 weeks' gestation. Importantly, our results suggest that this improved survival was not associated with an increased risk of NDI. The small size of the GA subgroup ≥27 weeks and the consequently wide CI provide too little information for inference about the treatment effect in this subgroup.

For further inspection, we used post hoc STEPP analysis to explore the effect of hydrocortisone along the continuum of GA, respiratory index and the probability of moderate/severe BPD or death. STEPP has the advantage over the more conventional approach of categorisation of a continuous covariate, that it provides more insight into the effect along the range of covariate values, and where treatment may be particularly beneficial (or detrimental). STEPP is an exploratory tool, not intended to set specific cut-off points for subgroups, but rather to provide some indication on ranges of values where the treatment effect might have a particular behaviour.[17 18] Hence, it facilitates hypothesis generation and provides guidance for future research. The STEPP of treatment effect heterogeneity for GA supported the results of the prespecified dichotomised subgroup analysis, though not statistically significant. Additional analyses of treatment effect heterogeneity for GA should be considered in other studies of hydrocortisone treatment.

In daily practice, the decision to start postnatal corticosteroids is often guided by the severity of the patients' respiratory condition and the presumed risk of BPD. This is probably based on a meta-regression analysis of randomised controlled trials investigating dexamethasone that suggests that the effect of postnatal corticosteroids on the combined outcome death or cerebral palsy varies with the underlying baseline risk of BPD. Infants at higher risk of BPD seem to benefit from postnatal dexamethasone treatment, while treating infants at low risk of BPD might be harmful.[16] We found no clear treatment effect heterogeneity for the key long-term composite outcome and its components across the range of probabilities for moderate/severe BPD or death, calculated with the NICHD Neonatal BPD Outcome Estimator.[15] This lack of treatment effect heterogeneity may partly be explained by the fact that the SToP-BPD Study included ventilator-dependent very preterm infants with a respiratory index above 2.5. These criteria resulted in a narrow distribution of the probabilities of moderate/severe BPD or death as almost

all infants in our study were classified as high risk. Furthermore, the NICHD Neonatal BPD Outcome Estimator is based on the US population and is not yet validated in the Dutch/Belgian population, so it remains unclear how it will perform in the SToP-BPD Study population. Additional analyses for heterogeneity of the hydrocortisone treatment effect are needed in other clinical studies to gain more insight.

Our study has some limitations. First, the SToP-BPD Study was only powered for the overall treatment effect on the primary composite outcome death or BPD at 36 weeks' PMA.[9] Due to the small numbers within various subgroups, there is limited statistical power to identify subgroups that might have a differential effect of hydrocortisone treatment. Also, except for the randomisation stratification factor GA, interpretation of the other subgroups is hampered by potential confounder imbalance. Therefore, this secondary analysis of the SToP-BPD Study should be regarded as exploratory and hypothesis generating only. Second, STEPP analysis is sensitive to the choices of subgroup sample size (r2) and overlap between subsequent subgroups (r1).[17 18] However, our sensitivity analyses with varying r1 and r2 showed similar patterns of heterogeneity. Third, a relatively high proportion of infants in the placebo group (56.8%) was treated with open-label hydrocortisone, particularly those with a GA below 27 weeks. Although no firm conclusions can be drawn, it is unlikely that this impacted the subgroup analyses, as a previous published meta-regression analysis showed no modulating effect of open-label steroids on long-term outcomes.[22]

CONCLUSIONS

This secondary analysis of the SToP-BPD trial suggests that in the subgroup of ventilated preterm infants born before 27 weeks' gestation, systemic hydrocortisone initiated in the second week after birth may improve the composite outcome death or NDI, mainly driven by its component death. There was insufficient evidence for the other selected candidate treatment effect modifiers. The findings of this study require confirmation in larger future trials.

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Contributors MS, RMS, CK-E, MvS, SM-dT, RNGBT, TM, EB, KS, BWK, AD, MMvW, YM, HG, KP, MO and AGvW-L 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 participated in the statistical analyses, and critically reviewed and revised the manuscript for important intellectual content. WO and AHvK are local investigators who 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. AHvK is the guarantor.

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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.

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 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).

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