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Influence of antenatal steroids on the effect of early inhaled postnatal corticosteroids: a post-hoc analysis of the NEuroSIS trial

Jehudith Fontijn[1*], Corinna Engel[2], Karen B. Kreutzer[3], Christian Poets[3] and Dirk Bassler[1]

Abstract

Background Few data are available on the interplay of antenatal and early inhaled postnatal corticosteroids. The NEuroSIS trial randomized extremely preterm infants to receive either early inhaled budesonide or placebo and analyzed the effect of study medication on bronchopulmonary dysplasia or death, as well as the effect on neurodevelopmental outcome at 18–22 months corrected age. Application of antenatal steroids may have had an influence on these outcomes.

Objective To analyze if antenatal corticosteroids (ANS) influenced the short- (BPD and death before 36 weeks PMA) and long-term (disability at 18–22 months corrected age or death before time of assessment) effects of early inhaled postnatal budesonide in NEuroSIS study participants.

Methods Post-hoc analysis of the intention-to-treat population of the NEuroSIS study. Generalized logits models were used to (1) predict risk of BPD, death before 36 weeks PMA and survival without BPD with application of ANS, NEuroSIS study treatment and gestational age as independent variables and (2) predict the risk of disability at 18–22 months corrected age, death before time of neurodevelopmental assessment and survival without disability, with ANS and gestational age as independent variables.

Results Application of ANS, added as an independent variable, did not change the effect of study medication on developing BPD (OR 0.79, 95% CI 0.67–0.93) and there was no association with the risk of death (OR 1.03, 95% CI 0.84–1.27) at 36 weeks PMA. ANS added as an independent variable showed an association with a reduced risk of death before time of completion of neurodevelopmental assessment (OR 0.60, 95% CI 0.44–0.81) and was associated with a reduced risk of disability at 18–22 months corrected age(OR 0.63, 95% CI 0.49–0.81).

Conclusion ANS did not alter the reduction of BPD risk by study medication and there was no association with increased mortality in NEuroSIS study participants.

Keywords Bronchopulmonary dysplasia, Death, Neurodevelopmental delay, Antenatal steroids, Early inhaled postnatal steroids, Budesonide

*Correspondence:
Jehudith Fontijn
jehudith.fontijn@usz.ch
[1]Department of Neonatology, University Hospital Zurich and University of Zurich, Frauenklinikstrasse 10, Zurich 8091, Switzerland
[2]Center for Pediatric Clinical Studies (CPCS), University Children's Hospital Tübingen, Tübingen, Germany
[3]Department of Neonatology, University Children's Hospital Tübingen, Tübingen, Germany

Background

Advances in the care of very preterm infants in the last decades have resulted in better survival. Despite this, bronchopulmonary dysplasia (BPD) remains one of the most relevant morbidities, showing an increase in incidence among extremely preterm infants [1]. BPD not only has an effect on long–term pulmonary but also on neurodevelopmental outcome, which makes prevention of BPD an important research subject [2–4]. Early inflammation is acknowledged as a major contributor to the pathogenesis of BPD. Cortisol is an important factor in controlling inflammation. Early (≤ 7 days after birth) BPD prevention with postnatal systemic corticosteroids, especially dexamethasone, is effective in preventing BPD, but significantly increases the risk of cerebral palsy and is therefore not an option as a preventive strategy [5]. The research focus thus shifted to BPD prevention with low–dose systemic hydrocortisone or inhaled corticosteroids. Low–dose early hydrocortisone treatment significantly increased BPD–free survival [6], inhaled budesonide significantly reduced the incidence of BPD as a prespecified secondary outcome [7]. Both preventive strategies did not influence neurodevelopmental outcome at 2 years or 18–22 months corrected age respectively [8, 9]. Still, the overall beneficial effect of early low-dose systemic or inhaled corticosteroid therapy is debated and benefit – risk adapted strategies remain subject to research [10, 11].

The introduction of antenatal corticosteroids (ANS) for fetal lung maturation had no effect on the rate of bronchopulmonary dysplasia in survivors [12, 13]. Meta-analysis did not confirm concerns regarding negative associations between ANS and neurodevelopmental outcome (developmental delay, cerebral palsy) [12]. Few data are available on the interplay of antenatal and early inhaled postnatal corticosteroids. In the NEuroSIS trial, an international randomized clinical trial, coordinated by the University Hospital in Tübingen, Germany, extremely preterm infants were randomized to either early inhaled budesonide or placebo. The primary objective of this post–hoc analysis was to analyze the possible influence of ANS on short-term (BPD and death before time of BPD assessment) effect of the NEuroSIS study medication. The secondary objective was to analyze the potential influence of ANS on long-term (disability at 18–22 months corrected age or death before time of neurodevelopmental assessment) effect of NEuroSIS study medication.

Methods

The original publication of the NEuroSIS Study reports the detailed trial design as well as the a priori primary and secondary outcomes of this multinational, randomized trial [7, 9]. The research ethics board at the University Hospital Tübingen and each participating center approved the trial. Written informed consent from parents or guardians was obtained before randomization. Summarized, the NEuroSIS study included infants with a gestational age of 23 weeks 0 days to 27 weeks 6 days and a chronological age up to 12 h who required any form of positive-pressure respiratory support. Study participants were randomly assigned to early treatment with inhaled budesonide or placebo. Application of study drugs (400 µg budesonide every 12 h via a metered–dose inhaler connected to a spacer, from day 15 onwards 200 µg budesonide every 12 h), started within 24 h after birth and discontinued at a postmenstrual age of 32 weeks 0 days or once there was no further requirement of positive-pressure support or supplemental oxygen for at least 72 h. The a priori primary composite outcome was death or BPD before 36 weeks PMA. Neurodevelopmental disability tested at 18 to 22 months corrected age was a major a priori secondary outcome [7, 9]. BPD was defined as the requirement of positive-pressure support, supplemental oxygen at a fraction of inspired oxygen exceeding 0.30 or, in infants receiving low amounts of oxygen, an inability to maintain an oxygen saturation level above 90% during an oxygen-reduction test at 36 weeks PMA. For the primary outcome, death was defined as death of any cause before 36 weeks PMA. Neurodevelopmental disability was defined as a composite of cerebral palsy, cognitive delay (a Mental Developmental Index score of < 85 on the Bayley Scale of Infants Development, Second Edition), deafness or blindness at 18 to 22 months corrected age. For the current post-hoc analysis, we analyzed the data of the 856 infants enrolled in the original study (intention-to-treat population of the NEuroSIS study, randomization and stratification according to gestational age preserved) including the collected data on the administration of ANS to the mother. We defined a full course of ANS as any corticosteroid recommended for antenatal treatment to accelerate fetal organ maturation, the first dose given at least 48 h before birth. Definitions for BPD and neurodevelopmental disability were the same as in the original study. We defined death as death before the time of assessment of the specific outcome (BPD or disability at 18–22 months corrected age respectively). As primary outcome of this post–hoc analysis, we defined the influence of ANS on the short-term, mutually exclusive outcomes BPD, death before 36 weeks PMA and survival without BPD, corrected for the influence of study medication and gestational age below 26 weeks. As secondary outcome, we defined the influence of ANS on the long-term, mutual exclusive outcomes disability, death before time of neurodevelopmental assessment and survival without disability. For the long-term outcome, the effect of ANS was corrected only for gestational age below 26 weeks, since the study medication did

Table 1 Baseline characteristics

	at least one complete course of ANS (*n* = 589)	one incomplete course of ANS (*n* = 182)	no ANS (*n* = 84)	ANS unknown (*n* = 1)	all (*n* = 856)
Characteristic					
Gestational age – wk mean (± SD)	26.2 (± 1.2)	25.9 (± 1.3)	25.7 (± 1.4)	23.7	26.1 (± 1.2)
Birthweight – g mean (± SD)	786 (± 192)	843 (± 192)	812 (± 172)	645	800 (± 191)
Male sex – no. (%)	290 (49.2)	98 (53.9)	46 (54.8)	1 (100)	435 (50.8)
Multiple birth – no. (%)	114 (19.4)	37 (20.3)	22 (26.2)	1 (100)	174 (20.3)
Born in study center – no. (%)	582 (98.8)	172 (94.5)	78 (92.9)	1 (100)	833 (7.3)

Table 2 Generalized logits model for the association of antenatal corticosteroids, NEuroSIS study treatment and gestational age on the mutually exclusive endpoints BPD, death and survival without BPD

independent factors	survival without BPD*	BPD		death		overall *p*-value
	no.	no.	OR (95% CI)	no.	OR (95% CI)	
antenatal corticosteroids						
at least one complete course	332	182	**1.34 (1.03–1.71)**	75	0.76 (0.57–1.01)	**0.004**
incomplete course	112	37	0.74 (0.54–1.01)	33	0.87 (0.62–1.22)	
none*	43	19		22		
NEuroSIS study group						
treatment	262	101	**0.79 (0.67–0.93)**	73	1.03 (0.84–1.27)	**0.007**
placebo*	225	137		57		
gestational age group						
23 wk 0 days to 25 wk 6 days	145	120	**1.57 (1.34–1.85)**	92	**2.36 (1.91–2.92)**	**< 0.0001**
26 wk 0 days to 27 wk 6 days*	342	118		38		

*reference category

not show an influence on the long–term outcomes death and disability.

Statistical analysis

The two endpoints with three mutually exclusive responses as described above were analyzed using generalized logits model. Odds ratios were calculated from the coefficients [14]. Possible influences on the two endpoints were analyzed including the following factors: ANS (none versus one or more incomplete courses versus at least one complete course), gestational age (≥ 26 weeks versus < 26 weeks) and study treatment (placebo versus inhaled budesonide). The distribution of the item of interest "ANS" within the three outcome options, respectively, is presented within a table for each endpoint. Odds ratios for the influence of "ANS given" are only presented based on "no ANS given". Dummy coding was not done to avoid confusing results. In case of *p*-values < 0.05, parameters were tested for possible interactions.

Results

Post-hoc primary outcome

We excluded one patient from the original ITT-population ($N = 856$) due to missing values concerning administration of ANS and therefore included 855 infants. There were no relevant differences between the ANS groups (complete course, incomplete course, no steroids) in any of the baseline characteristics (Table 1). Appendix 1 shows the distribution of ANS and study medication within the three post-hoc primary outcome groups. 589/855 infants were exposed to a full course of ANS, 182/855 to an incomplete course and 84/855 infants were not exposed to ANS at all. Results of multivariate analyses concerning the influence of ANS, study medication and gestational age on the post-hoc primary outcome are presented in Table 2. Receiving at least one full course of ANS was associated with a slight increase in the risk of BPD (OR 1.34, 95% CI 1.03–1.71 (*p*-value 0.03) compared to no ANS. NEuroSIS study treatment was associated with a lower risk of having BPD (OR 0.79, 95% CI 0.67–0.93 (*p*-value 0.004). Gestational age below 26 weeks showed the strongest association with the risk of developing BPD (OR 1.57, 95% CI 1.34–1.85 (*p*-value < 0.0001). Lower gestational age was strongly associated with the risk of death at 36 weeks PMA (OR 2.36, 95% CI 1.91–2.92, *p*-value < 0.0001), administration of any amount of ANS showed a trend towards a reduced risk of death before 36 weeks PMA. NEuroSIS study medication did not have an influence on death in this analysis (OR 1.03, 95% CI 0.84–1.27).

Table 3 Generalized logits model for the association of antenatal corticosteroids and gestational age on the mutually exclusive endpoints disability, death and survival without disability

independent factors	survival without disability*	disability		death		overall *p*-value
	no.	no.	OR (95% CI)	no.	OR (95% CI)	
antenatal corticosteroids						
at least one complete course	244	199	**0.63 (0.49–0.81)**	84	**0.6 (0.44–0.81)**	**0.003**
incomplete course	59	77	0.99 (0.74–1.34)	33	0.89 (0.62–1.3)	
none*	18	38		22		
gestational age group						
23 wk 0 days to 25 wk 6 days	106	127	1.15 (0.98–1.36)	96	**2.1 (1.68–2.59)**	**< 0.0001**
26 wk 0 days to 27 wk 6 days*	215	187		43		

*reference category

Post-hoc secondary outcome

Of the 856 infants of the ITT - population from the original NEuroSIS study, 43 infants were lost to follow–up (813 infants in ITT follow-Up population) [9]. 39 infants had to be excluded due to incomplete data. Therefore, adequate data were available in 774 cases. The results of the multivariate analyses concerning the post-hoc secondary outcome are presented in Table 3. Since NEuroSIS study medication did not reveal an impact on long–term outcome, we excluded study medication as an independent factor from the model. Receiving at least one full course of ANS was associated with a lower risk of disability (OR 0.63, 95% CI 0.49–0.81 (p–value 0.0003) and a lower risk of death before completion of follow–up compared to no ANS (OR 0.6, 95% CI 0.44–0.81 (p–value 0.001). Incomplete courses showed a trend towards reduction of death before completion of follow–up. Gestational age below 26 weeks was associated with a higher risk of death before completion of follow–up (OR 2.1, 95% CI 1.68–2.59 (p–value < 0.0001), whereas there was no relevant association with disability in this analysis. For *p*-values < 0.05, parameters were tested for possible interactions. We found no interactions between parameters.

Discussion

Post-hoc primary outcome

In this post–hoc analysis, application of ANS added as an independent variable, did not change the positive effect of the NEuroSIS study treatment on the development of BPD. In fact, to receive at least one complete course of ANS showed an association with a slightly raised risk of BPD. Regarding mortality, a full course of ANS reduced the risk of death at time of assessment while gestational age below 26 weeks increased it. Study treatment did not have an effect on mortality before BPD assessment, when corrected for application of ANS and gestational age. In a Cochrane analysis from 2020 about ANS for accelerating fetal lung maturation, the effect of ANS on chronic lung disease, compared to placebo or no treatment, remained unclear [12]. One possible explanation could be the significant reduction in rate of death in preterm infants below 29 weeks of gestation after exposure to ANS, thereby exposing more infants to the risk of developing BPD [13]. We observed this effect in our post-hoc analysis as a trend to lower mortality before 36 weeks PMA. A further potential explanation for this effect could be the lower baseline cortisol levels on the first postnatal day after application of ANS [10, 15]. High cortisol levels are associated with an increased BPD-free survival in extremely preterm infants [10, 16], where this effect was no longer observed when hydrocortisone was supplemented [10]. There are few reports on cortisol levels in preterm infants after treatment with inhaled budesonide. An older report from Bauer et al. [17] reported lower salivary cortisol levels after application of budesonide 100 µg/kg/day to infants born below 32 weeks of gestation during their fourth postnatal week. The dosing regimen of the NEuroSIS study was mainly based on the Open Study of Early Corticosteroid Treatment [18], comparing early glucocorticoid treatment with late treatment as well as dexamethasone with inhaled budesonide in infants below 30 weeks of gestation. This study did not find differences in complications of prematurity and treatment by group allocations. In participants of the NEuroSIS study, no cortisol levels were measured. We can only speculate that NEuroSIS study medication might have had some systemic anti-inflammatory effect, thereby explaining the reduction in BPD and compensating for the lower baseline cortisol levels on the first postnatal day after application of ANS. The trend to an enhanced risk of BPD after application of a full course of ANS was not powerful enough to change the association of NEuroSIS study medication with BPD reduction in the final model.

The original results of the NEuroSIS study reported a nonsignificant trend towards higher mortality in the treatment group at time of BPD assessment [7]. The authors discuss the possibility that the reduction of BPD in infants receiving budesonide might be acquired at the expense of a lower survival rate. A secondary analysis of the NEuroSIS study (Appendix to ref. 7) performed by logistic regression and adjusted for covariates, showed

no signal of budesonide upon death. In the model used in our post-hoc analysis, corrected for application of ANS and gestational age below 26 weeks, again no association with death was found. Although design limitations of this analysis do not allow us to draw explicit conclusions, these findings would support the effect of budesonide in reducing BPD.

Post-hoc secondary outcome

Neurodevelopmental outcome among survivors assessed at 18–22 months corrected age was one of the prespecified secondary outcomes of the NEuroSIS study [9]. Neurodevelopmental outcome did not differ between infants in the study treatment and placebo group. This was the argument to exclude study treatment as an independent variable in the analysis of our secondary objective, so no further thoughts can be spent on possible interactions between ANS and study medication regarding neurodevelopmental outcome. Application of ANS and gestational age below 26 weeks remained as independent variables in the model and since the associations found are equivalent to the known effects of ANS and low gestational age, these findings do not require further discussion [12]. While ANS was associated with a reduction in the risk of death before time of neurodevelopmental assessment at 18–22 months corrected age, gestational age below 26 weeks was associated with an increased risk. Since most deceased infants, (130 of 139), died before time of BPD assessment, the association between ANS and death before time of neurodevelopmental assessment largely reflects the association of ANS and death before BPD assessment. In the secondary multivariate logistic regression analysis of the NEuroSIS study (Appendix to ref. 7), pre-specified variables as possible candidates influencing the primary endpoints, mortality or bronchopulmonary dysplasia, were included. Since no significant interactions were found in this model, we decided for the current post-hoc analysis only to adjust for the stratification factor (gestational age) and the two key factors of our current question: ANS and study treatment. In contrast to the original study, we did not use composite outcomes in this post-hoc analysis. The argument to use combined outcomes, as used in the original study, is the fact of competitive risks, to prevent possible improvement of the condition (in this case BPD) to occur at the expense of an increased mortality. Engel et al. explained the arguments for this alternative analysis approach in a study published in 2016 [19]. The effects of interest, in this case BPD and disability, are competing with the other outcomes death or survival without BPD or disability. Because competing risks can result in changes in the opposite direction, as was the case in the original analysis of the NEuroSIS study, there is a possibility of failing to reach significant results in intervention studies using combined outcomes. This was an argument in the choice for the statistical approach of this current post-hoc analysis. Since our results can only show associations, the results of the original NEuroSIS study, where, despite various ways of analyzing the data, uncertainty remains regarding the trend in increased mortality after exposure to study medication, should be disclosed in discussions about treatment options for extremely premature infants at risk of BPD.

There are several limitations to this study. First, this is a post-hoc analysis where we did not account for multiple testing. Thereby our study results can only be used for generating hypothesis. Secondly, the definition used for full exposure to ANS differs between studies. Where Norman et al. [20] report relevant positive effects of ANS as early as 3 h after the first dose, other studies defined a complete course only as 24 h after the first dose. This heterogeneity between definitions can be a disturbing factor in comparisons between studies. As a third limitation, we have to take into consideration that 43 infants were lost to follow-up and from 39 infants data on follow-up were incomplete, thereby theoretically creating a bias in the interpretation of disability at 18–22 months corrected age as well as death before neurodevelopmental assessment. Further, we acknowledge the problem of generalizability of the trial findings to the overall population, since the original trial enrolled 49% of the eligible population and our post-hoc analysis was done on the ITT population of the original study.

Conclusion

In summary, ANS did not alter the reduction of BPD risk by study medication and there was no association with increased mortality in NEuroSIS study participants.

Abbreviations

BPD	Bronchopulmonary dysplasia
ANS	Antenatal steroid
ITT	Intention to treat
OR	Odds ratio
CI	Confidence interval

Supplementary information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-025-05512-z.

Supplementary Material 1

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Not applicable.

Author contributions

Jehudith Fontijn contributed to the conceptualization, methodology, formal analysis, wrote the original draft and reviewed, edited and validated the draft. Corinna Engel contributed to the methodology and formal analysis, reviewed, edited and validated the draft. Karen B. Kreutzer reviewed, edited and validated the draft. Christian Poets reviewed, edited and validated the draft.

Dirk Bassler contributed to the conceptualization and methodology, reviewed, edited and validated the draft and fulfilled supervising tasks. All authors approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability
Data is provided within the manuscript or supplementary information files. The original data were generated in the original NEuroSIS publications (ref. 7 and 9).

Declarations

Ethics approval and consent to participate
The original NEuroSIS trial was designed in accordance with the Declaration of Helsinki and approved by the research ethics board at University Hospital, Tübingen, and at each of the participating centers.

Human ethics and consent to participate
Not applicable for this post-hoc analysis. For the original NEuroSIS trial appropriate regulatory approvals and written informed consent from parents or guardians were obtained before randomization.

Clinical trial number
Not applicable for this post-hoc analysis. ClinicalTrials.gov number of the original NEuroSIS trial NCT01035190.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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