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Intratracheal Budesonide Mixed With Surfactant for Extremely Preterm Infants
The PLUSS Randomized Clinical Trial

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IMPORTANCE Bronchopulmonary dysplasia (BPD) is a common adverse outcome in extremely preterm infants born at less than 28 weeks' gestation. Systemic corticosteroids are effective against BPD but may be associated with adverse outcomes. Corticosteroids given directly into the lungs may be effective and safer.

OBJECTIVE To investigate the effectiveness of early intratracheal corticosteroid administration on survival free of BPD in extremely preterm infants.

DESIGN, SETTING, AND PARTICIPANTS Double-blind randomized clinical trial conducted in 21 neonatal units in 4 countries (Australia, New Zealand, Canada, and Singapore), enrolling infants born at less than 28 weeks' gestation and less than 48 hours old who were mechanically ventilated (regardless of ventilator settings or oxygen requirements) or who were receiving noninvasive respiratory support and had a clinical decision to treat with surfactant. Recruitment occurred from January 2018 to March 2023. The last participant was discharged from the hospital in August 2023.

INTERVENTIONS Infants were randomly allocated (1:1) to receive budesonide, 0.25 mg/kg, mixed with surfactant (poractant alfa), administered via an endotracheal tube or thin catheter, or surfactant only.

MAIN OUTCOMES AND MEASURES The primary outcome was survival free of BPD at 36 weeks' postmenstrual age. There were 15 secondary outcomes, including the 2 components of the primary outcome (survival at 36 weeks and BPD among survivors), and 9 predefined safety outcomes (adverse events).

RESULTS The primary analysis included 1059 infants, 524 in the budesonide and surfactant group and 535 in the surfactant-only group. Overall, infants had a mean gestational age of 25.6 weeks (SD, 1.3 weeks) and a mean birth weight of 775 g (SD, 197 g); 586 (55.3%) were male. Survival free of BPD occurred in 134 infants (25.6%) in the budesonide and surfactant group and 121 infants (22.6%) in the surfactant-only group (adjusted risk difference, 2.7% [95% CI, −2.1% to 7.4%]). At 36 weeks' postmenstrual age, 83.2% of infants were alive in the budesonide and surfactant group and 80.6% in the surfactant-only group. Of these, 69.3% and 71.9% were diagnosed with BPD, respectively.

CONCLUSIONS AND RELEVANCE In extremely preterm infants receiving surfactant for respiratory distress syndrome, early intratracheal budesonide may have little to no effect on survival free of BPD.

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Preterm birth remains the greatest cause of neonatal mortality and morbidity, with infants born extremely preterm before 28 weeks' gestation (approximately 600 000 per year worldwide) at highest risk.[1] With modern intensive care, 85% of infants born extremely preterm survive, but more than half develop bronchopulmonary dysplasia (BPD).[2,3] Compared with those without BPD, survivors with BPD are at greater risk of early childhood respiratory illnesses, asthma, and adverse neurodevelopmental outcomes.[4] With BPD rates increasing[2,5] and very few therapies that safely reduce its incidence, prevention of BPD is a major global research priority.[6]

Anti-inflammatory corticosteroids have been the focus of preventive interventions for BPD, but the optimal regimen, including route of administration, remains unclear. Although systemic (intravenous or enteral) corticosteroids reduce BPD risk, when they are administered in the first week after birth or at a high cumulative dose, they are associated with harm, including increased risk of cerebral palsy in survivors.[7] Similarly, prolonged neonatal courses of inhaled corticosteroids (eg, via a metered dose inhaler) have been associated with increased mortality.[8,9] Direct tracheal installation of low-dose corticosteroid using exogenous surfactant as a vehicle has shown promise in preclinical animal studies, in which it reduced lung inflammation and injury and improved lung function without negative effects on the efficacy of surfactant.[10-15]

Two previous randomized clinical trials, with a combined total sample size of 381, enrolled mechanically ventilated very low-birth-weight infants (<1500 g) who were receiving relatively high levels of supplemental oxygen: a fraction of inspired oxygen (F_{IO_2}) of 50% or greater in one trial and 60% or greater in the other.[16,17] These trials reported that intratracheal budesonide, 0.25 mg/kg, mixed with surfactant, compared with surfactant only, was associated with a more than one-third reduced risk in the combined outcome of death or BPD.[16-18] Neurodevelopmental impairment at 2 to 3 years of age was also potentially reduced in one of these trials.[16] Based on these findings, some centers have introduced intratracheal budesonide into routine care.[19] However, a large pragmatic trial to assess the effectiveness of this therapy across a broader group of extremely preterm infants has been needed to guide international practice, including the smallest and highest-risk infants and those receiving noninvasive respiratory support.

The current trial, Preventing Lung Disease Using Surfactant + Steroid (PLUSS), was undertaken to determine whether intratracheal budesonide mixed with surfactant benefits extremely preterm infants. It tested the hypothesis that in infants born extremely preterm who were receiving surfactant for respiratory distress syndrome in the first 48 hours after birth, intratracheal budesonide would increase survival free of BPD at 36 weeks' postmenstrual age (PMA) compared with infants treated with surfactant only.

Key Points

Question What is the effect of intratracheal budesonide mixed with surfactant on survival free of bronchopulmonary dysplasia in infants born extremely preterm (<28 weeks' gestation)?

Findings In this international randomized clinical trial of 1059 extremely preterm infants, there was no clear difference in survival free of bronchopulmonary dysplasia between infants who received intratracheal budesonide mixed with surfactant and those who received surfactant only (25.6% vs 22.6%; adjusted risk difference, 2.7% [95% CI, −2.1% to 7.4%]).

Meaning In extremely preterm infants receiving surfactant, early intratracheal budesonide may have little to no effect on survival free of bronchopulmonary dysplasia.

Methods

Trial Design and Oversight

The PLUSS trial was a multicenter, double-blind, 2-group, parallel randomized clinical trial conducted according to a published protocol[20] in 21 neonatal intensive care units (NICUs) in 4 countries (14 in Australia, 5 in New Zealand, and 1 each in Singapore and Canada) (see Supplement 1 for the final trial protocol). The trial was approved by the Royal Children's Hospital Human Research Ethics Committee, Melbourne, Australia, as well as the relevant local ethics committee in each jurisdiction (eAppendix 1 in Supplement 2). Parents or guardians provided written informed consent for their infant(s) antenatally or postnatally. The trial was overseen by an external data and safety monitoring board (DSMB; members are listed in eAppendix 2 in Supplement 2) who undertook 5 interim safety analyses through the trial and a single analysis for efficacy at the halfway point of recruitment. At all time points, the DSMB recommended that the trial continue unchanged. This report follows the Consolidated Standards of Reporting Trials (CONSORT) guideline.

Participants

Infants were eligible if they were born at less than 28 weeks' gestation; they were less than 48 hours of age; and they were either (1) receiving mechanical ventilation via an endotracheal tube or (2) receiving noninvasive respiratory support (including nasal continuous positive airway pressure, nasal intermittent positive pressure ventilation, or nasal high flow) and there was a clinical decision to treat with surfactant for respiratory distress syndrome (there were no set trial criteria for this decision to treat with surfactant). Infants remained eligible for enrollment if they had already received no more than 1 dose of exogenous surfactant. These infants were assessed 6 to 12 hours after their first surfactant dose, and if they satisfied the above criteria, they were eligible. This design choice aimed to ensure that as many extremely preterm infants as possible were eligible for the trial and to minimize selection bias. Maternal ethnicity was self-reported; this outcome was included because the effect of the intervention and adverse outcomes of extremely preterm birth may differ by ethnicity, and to aid the interpretation of results by clinicians in different regions.

Exclusion criteria included prior treatment with postnatal corticosteroids for prevention of lung disease (inhaled, nebulized, intratracheal, or systemic); survival beyond the

immediate postnatal period considered unlikely and/or active care not offered; transfer to a nonparticipating NICU considered likely within 24 hours of birth; or presence of known or suspected major congenital anomaly likely to affect respiratory status, including a postnatal clinical diagnosis of severe pulmonary hypoplasia not believed to be survivable.

Randomization

The allocation sequence was computer generated in a 1:1 ratio using balanced, random permuted block sizes, stratified by study center, gestational age (22-25 weeks' vs 26-27 weeks' completed gestation), prior surfactant therapy, and mode of respiratory support at randomization (mechanical ventilation via an endotracheal tube vs noninvasive respiratory support). Web-based randomization was performed via the Research Electronic Data Capture (REDCap) randomization tool, which assigned an opaque numbered envelope containing treatment allocation.[21,22] The allocation sequence was not known to anyone associated with the study. Infants from multiple pregnancy were randomized individually.

Trial Interventions

The study interventions were provided in the delivery room or NICU. The budesonide and surfactant group (active intervention) received 1 or 2 doses of budesonide, 0.25 mg/kg, mixed with poractant alfa (200 mg/kg for first dose; 100 mg/kg for second dose, if used), administered intratracheally. The first dose was administered as soon as possible after randomization. A second dose was given if an infant still met eligibility criteria 6 to 12 hours after the first dose (infants could be older than 48 hours at this point). The budesonide dose was based on published trials.[16,23] The surfactant-only group (control intervention) received identical doses of poractant alfa alone.

To ensure that treating clinicians, investigators, parents or caregivers, and outcome assessors were blinded to interventions, a 2-person intervention team was convened from on-duty staff who were not involved in the clinical care of a study infant to open the sealed, opaque randomization envelope in a private space and prepare the trial intervention. The intervention team then covered the administration syringe with an opaque sticker before approaching the cot side, where the intervention was administered to the infant. The intervention team deposited open envelopes in a locked box, accessible only to the local trial pharmacist. The following methods of intratracheal instillation were permitted: standard bolus administration through an endotracheal tube that remained in situ with ongoing mechanical ventilation, the INSURE (intubate, surfactant, extubate) technique via an endotracheal tube, or administration via a thin catheter to infants receiving noninvasive respiratory support ("less" or "minimally" invasive surfactant administration technique[24,25]).

Inhaled or nebulized corticosteroid treatment was not permitted until after the primary outcome had been determined (ie, 36 weeks' PMA). All other management after randomization was at the discretion of the clinical team. Postnatal systemic corticosteroid treatment was based on local guidelines.

Trial Outcomes

The primary outcome was survival without physiological BPD, assessed between 36 weeks 0 days' and 36 weeks 6 days' gestation, defined by 1 or more of the following criteria:

1. Receiving mechanical ventilation via an endotracheal tube, continuous positive airway pressure, nasal intermittent positive pressure ventilation, or nasal high flow at 2 L/min or greater, regardless of F_{IO_2}
2. An effective F_{IO_2} of 0.30 or greater, determined using the Benaron-Benitz formula,[26] if receiving supplemental ambient oxygen or nasal prong flow at less than 2 L/min to maintain target oxygen saturations
3. An effective F_{IO_2} of less than 0.30 if receiving supplemental ambient oxygen or nasal prong flow at less than 2 L/min to maintain target oxygen saturations *and* an unsuccessful air reduction trial

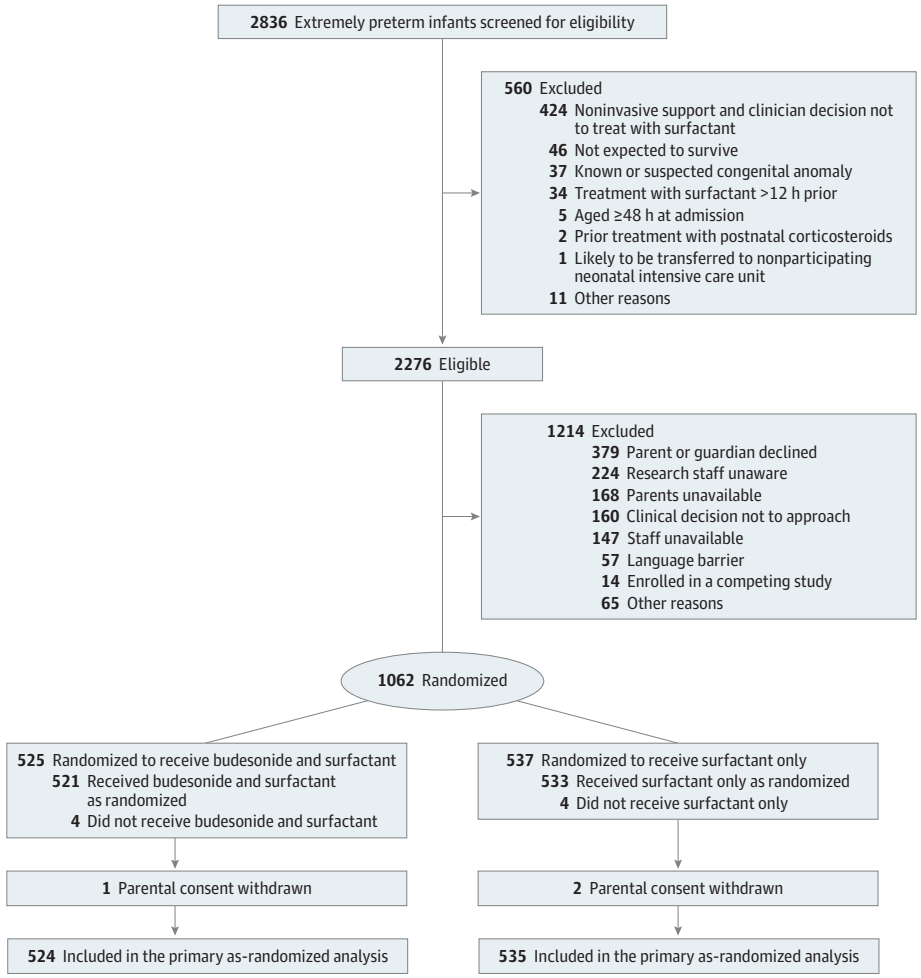
Infants who were discharged home prior to 36 weeks 0 days' PMA without any respiratory support or supplemental oxygen were classified as having no BPD. For infants in whom the BPD assessment was incorrectly or inadequately performed (eg, too early, too late, or incomplete data) the trial steering committee (members are listed in eAppendix 2 in Supplement 2) approved an algorithm for determining a diagnosis of BPD. This algorithm used data collected at exactly 36 weeks 0 days' PMA, and assessors were blinded to study group allocation (eTable 3 in Supplement 2).

Secondary trial outcomes included the outcomes of survival at 36 weeks' PMA and survival with BPD that contributed to the primary outcome, along with prespecified in-hospital outcomes and adverse events[20,27] (eAppendix 3 in Supplement 2). BPD grade (severity) was defined according to the 2019 criteria of Jensen et al,[28] which are based on the type of respiratory support being received by an infant at 36 weeks' PMA, regardless of prior or current supplemental oxygen therapy: no BPD and no support; grade 1 BPD (least severe) with nasal cannula 2 L/min or less; grade 2 BPD with nasal cannula greater than 2 L/min or noninvasive positive airway pressure; and grade 3 (most severe) BPD with invasive mechanical ventilation. Serious adverse events of interest for the purposes of this trial were (1) death before hospital discharge; (2) spontaneous intestinal perforation (perforation not associated with necrotizing enterocolitis or other known pathology); and (3) receipt of cardiopulmonary resuscitation (chest compressions) and/or administration of adrenaline/epinephrine (for resuscitation) within 24 hours of the intervention.

Sample Size Estimation and Statistical Analysis

A detailed statistical analysis plan for the PLUSS trial has been published.[27] The estimated risk of the primary outcome of survival free of BPD was 50%, based on data from the lead center (The Royal Women's Hospital, Melbourne, Australia) and published studies enrolling extremely preterm infants.[8,29] A sample size of 1038 infants (519 in each group) was required to provide 90% power to detect an absolute increase in survival free of BPD of 10%, with a 2-tailed $\alpha = .05$. To account for any losses, the trial aimed to recruit 1060 infants (530 infants in each group).

Figure 1. Participant Flow Through the PLUSS Trial



The primary analysis included all randomized infants, regardless of exposure to the allocated treatment or adherence to the trial protocol, excluding infants whose parents withdrew them from the trial and did not provide consent to use study data. In the primary analysis, the primary and secondary outcomes were compared between intervention groups using risk differences for binary outcomes, estimated by generalized linear models (binomial distribution with identity link function); mean differences for continuous outcomes, estimated by linear regression; or median differences for skewed continuous data, estimated using quantile regression, with 95% CIs (Stata software version 18; StataCorp). The primary outcome models were adjusted for the stratification factors used in the randomization (gestational age, prior receipt of surfactant, and mode of respiratory support). For the secondary outcomes, there was no adjustment for stratification variables. Standard errors for all models were adjusted to take into account the clustering of infants from multiple pregnancy. Prespecified exploratory analyses of the primary outcome included subgroup analyses for randomization strata, sex, small-for-gestational-age birth weight (<10th percentile for gestational age and sex),[30] and presence of chorioamnionitis. A post hoc subgroup analysis based on baseline FIO_2 (≥0.50 or <0.50) was also performed.

Results

Trial Population

Recruitment occurred from January 2018 to March 2023; the last infant was discharged from the hospital in August 2023. A total of 2836 extremely preterm infants were assessed for eligibility (**Figure 1**). There were 560 infants who did not meet inclusion criteria, and a further 1214 were not enrolled or consented, leaving a final sample of 1062 infants. Three infants were subsequently withdrawn from the study, resulting in an intention-to-treat analysis population of 1059 infants, 524 in the budesonide and surfactant group and 535 in the surfactant-only group (Figure 1).

The demographic and clinical characteristics were similar between the groups (**Table 1**). Overall, infants had a mean gestational age of 25.6 weeks (SD, 1.3 weeks) and a mean birth weight of 775 g (SD, 197 g); 586 (55.3%) were male. Almost all infants in each group had been exposed to antenatal

Table 1. Maternal and Infant Baseline Demographic and Clinical Characteristics

Characteristics	Budesonide and surfactant (n = 524)	Surfactant only (n = 535)
Maternal characteristics		
Age at delivery, mean (SD), y	31.1 (6.3)	30.9 (5.9)
Primary ethnicity, No. (%)[a]		
Aboriginal or Torres Strait Islander	29 (5.5)	29 (5.4)
African or Indigenous	17 (3.2)	13 (2.4)
Asian	96 (18.3)	113 (21.1)
Caucasian	313 (59.7)	300 (56.1)
First Nations, Ink/Inuit, and/or Metis (Canada)	4 (0.8)	9 (1.7)
Hispanic	4 (0.8)	6 (1.1)
Māori	40 (7.6)	37 (6.9)
Pacific Islander	20 (3.8)	24 (4.5)
Other ethnicity	1 (0.2)	4 (0.7)
Exposure to any antenatal corticosteroids, No. (%)[b]	501 (95.6)	515 (96.3)
Exposure to a full course of antenatal corticosteroids, No. (%)[b]	351 (67.0)	354 (66.2)
Treatment with magnesium sulfate for fetal neuroprotection, No. (%)	442 (84.4)	450 (84.1)
Hypertensive disorders of pregnancy, No. (%)[c]	64 (12.2)	86 (16.0)
Chorioamnionitis, No. (%)		
Clinical	110 (21.0)	109 (20.4)
Histological[d]	212/494 (42.9)	227/494 (46.0)
Prolonged rupture of membranes >18 h, No. (%)	154 (29.3)	175 (32.7)
Labor, No. (%)	330 (63.0)	329 (61.5)
Cesarean delivery, No. (%)[e]	328 (62.5)	353 (65.9)

(continued)

corticosteroids. Further information on the representativeness of the enrolled population can be found in eTable 5 in Supplement 2. Fifty-seven percent of infants received surfactant treatment prior to randomization, and these infants, compared with those who did not receive prior surfactant, were less likely to be exposed to a full course of antenatal corticosteroids, were nearly a week more immature, and were more likely to be intubated in the delivery room (83.7% vs 34.5%) and receive ongoing mechanical ventilation (94.2% vs 49.1%), indicating that they had an earlier and more severe form of respiratory distress syndrome (eTable 2 in Supplement 2). The subgroup of infants who had not received prior surfactant were enrolled at a median age of 1 hour (IQR, 0-3 hours). Per the protocol, only infants who remained intubated or for whom there was a clinical decision to repeat surfactant treatment were eligible for a second trial intervention. This occurred in more than two-thirds of infants in the trial, 359 (68.5%) in the budesonide and surfactant group and 389 (72.7%) in the surfactant-only group. Eight infants (4 in each group) did not receive any trial intervention but were included in the intention-to-treat analysis. Both groups received a mean of 1.7 (SD, 0.5) interventions. The first trial intervention dose was given by a thin catheter in 14.2% of the budesonide and surfactant group and in 13.4% of the surfactant-only group, and by the INSURE technique using an endotracheal tube in 5.8% and 5.5%, respectively, with the remainder receiving the intervention during ongoing mechanical ventilation via an endotracheal tube.

Primary Outcome

Survival free of BPD occurred in 134 infants (25.6%) in the budesonide and surfactant group and 121 (22.6%) in the surfactant-only group (adjusted risk difference, 2.7% [95% CI, −2.1% to 7.4%]) (**Table 2**; unadjusted results in eTable 1 in Supplement 2). At 36 weeks' PMA, there were 436 infants (83.2%) alive in the budesonide and surfactant group, of whom 302 (69.3%) were diagnosed with BPD; in the surfactant-only group, 431 infants (80.6%) were alive, of whom 310 (71.9%) were diagnosed with BPD (for survival: adjusted risk difference, 1.4% [95% CI, −2.9% to 5.7%]; for BPD diagnosis: adjusted risk difference, −2.7% [95% CI, −8.4% to 3.1%]) (Table 2).

There was no evidence of an interaction between any of the prespecified subgroups and the treatment effect (**Figure 2**). There were 102 infants (11.8%) who had their BPD diagnosis made using the prespecified BPD algorithm (eTable 3 in Supplement 2). Detailed information on all infant deaths that occurred before discharge from the hospital is available in eTable 4 in Supplement 2. The most common cause of death in both groups was intraventricular hemorrhage; the second most common was infection. A Kaplan-Meier curve of survival up to hospital discharge or 52 weeks' PMA (whichever came first) is available in the eFigure in Supplement 2.

Secondary and Safety Outcomes

There were no clinically important differences in the risk of secondary outcomes between the budesonide and surfactant

Table 1. Maternal and Infant Baseline Demographic and Clinical Characteristics (continued)

Characteristics	Budesonide and surfactant (n = 524)	Surfactant only (n = 535)
Infant characteristics		
Gestational age, mean (SD), wk	25.7 (1.3)	25.6 (1.4)
Birth weight, median (IQR), g	768 (634-900)	740 (624-910)
Small-for-gestational-age birth weight (<10th percentile for gestation and sex)[30], No. (%)	73 (13.9)	74 (13.8)
Sex, No. (%)		
Female	236 (45.0)	237 (44.3)
Male	288 (55.0)	298 (55.7)
Multiple birth, No. (%)	133 (25.4)	163 (30.5)
Intubated in the delivery room, No. (%)	334 (63.7)	327 (61.1)
Apgar score at 5 min, median (IQR)[f]	7 (6-8)	7 (6-8)
Age at randomization, median (IQR), h	4.6 (1.0-8.0)	5.0 (1.0-8.0)
Mechanically ventilated via an endotracheal tube at randomization, No. (%)	391 (74.6)	400 (74.8)
Prior surfactant treatment, No. (%)	295 (56.3)	306 (57.2)
Other medications received prior to randomization, No. (%)		
Caffeine	339/523 (64.8)	350 (65.4)
Inotropes	42/523 (8.0)	44 (8.2)
Corticosteroids for hypotension	6 (1.1)	15 (2.8)
Blood gas analysis prior to randomization[g]		
pH, mean (SD)	7.29 (0.09) [n = 449]	7.29 (0.08) [n = 448]
Partial pressure of carbon dioxide, mean (SD), kPa	6.3 (1.4) [n = 450]	6.2 (1.5) [n = 453]
Blood glucose concentration, median (IQR), mg/dL	81 (59-108) [n = 444]	79 (58-108) [n = 451]
Fraction of inspired oxygen immediately prior to first intervention, median (IQR)[g]	0.30 (0.23-0.42) [n = 515]	0.30 (0.23-0.45) [n = 529]

SI conversion factor: To convert glucose to millimoles per liter, divide by 18.

[a] Maternal primary ethnicity was self-identified. Aboriginal or Torres Strait Islander: persons of Aboriginal or Torres Strait Islander descent. African or Indigenous: Afro-Caribbean, African Canadian, Indigenous African, or Native American. Asian: persons whose ethnic background originates from a country or countries in Asia, Southeast Asia, or the Indian subcontinent. Caucasian: persons of Caucasoid heritage, including Arabic, European, Russian, and Middle Eastern. Māori: persons of New Zealand Māori descent who identify as Māori. Pacific Islander: persons from Pacific Islander background, including Cook Islander, Niuean, Samoan, Tokelauan, Tongan, and other Pacific Islander groups.

[b] Maternal antenatal corticosteroids were given to accelerate fetal lung maturity. Given the large number receiving any antenatal steroids, the variable of exposure to a full course of antenatal steroids was added post hoc. A full course was defined as receiving at least 2 doses of antenatal corticosteroids.

[c] Hypertensive disorders of pregnancy include preeclampsia; eclampsia; and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. Preexisting hypertension is not included.

[d] Data on this variable were not available for all infants; in 70 cases, the placenta was not sent for histology, and 1 case had an unknown result. Sample sizes are shown in brackets.

[e] Some individuals went into labor prior to cesarean delivery.

[f] The Apgar score is a clinical indicator of an infant's condition in the minutes after birth. The score is based on 5 characteristics, skin color, heart rate, breathing, muscle tone, and reflex irritability. Each characteristic is assigned a score between 0 and 2 by a clinician, usually at 1 minute and 5 minutes after birth, with a total score between 0 (worst) and 10 (best). Healthy term infants are expected to have an Apgar score of 7 or higher at 5 minutes.

[g] Data on blood gas and fraction of inspired oxygen variables were not available for all infants; sample sizes are shown in brackets.

group and the surfactant-only group (Table 2). Notably, intratracheal budesonide did not reduce the duration of mechanical ventilation or hospitalization or the need for postnatal systemic corticosteroids or home oxygen. There were no significant differences in risk of serious adverse events between the groups (**Table 3**).

Post Hoc Analyses

The post hoc subgroup analysis to assess the influence of baseline FIO_2 on intervention effect (Figure 2) found that in the 226 infants receiving FIO_2 at 0.50 or greater immediately prior to the first trial intervention, the intratracheal budesonide and surfactant group had higher survival without BPD than the surfactant-only group (adjusted risk difference, 10.2% [95% CI, 1.5%-18.8%]). In contrast, this effect was not observed in the 418 infants receiving FIO_2 at less than 0.50 (adjusted risk difference, 0.4% [95% CI, −5.1% to 5.8%). However, the term for interaction between the intervention and baseline FIO_2 was not significant (P = .07).

Discussion

In this multicenter, double-blind randomized clinical trial in extremely preterm infants, we found no clear evidence that intratracheal budesonide mixed with surfactant, compared with surfactant only, increased the likelihood of survival free of BPD. However, a small clinical benefit cannot be entirely excluded, given the positive findings in previous trials[16,17] and the fact that the point estimate for the primary outcome of

Table 2. Primary and Secondary In-Hospital Outcomes

Outcomes	Budesonide and surfactant (n = 524)	Surfactant only (n = 535)	Risk difference, % (95% CI)
Primary outcome			
Survival free of BPD at 36 wk PMA, No. (%)[a]	134 (25.6)	121 (22.6)	2.7 (−2.1 to 7.4)[b]
Elements of the primary outcome			
Alive at 36 wk PMA, No. (%)	436 (83.2)	431 (80.6)	1.4 (−2.9 to 5.7)
BPD in survivors, No./total (%)	302/436 (69.3)	310/431 (71.9)	−2.7 (−8.4 to 3.1)
Other secondary outcomes			
Alive at hospital discharge, No. (%)	427 (81.5)	421 (78.7)	2.8 (−2.1 to 7.7)[c]
BPD grade in survivors at 36 wk, No./total (%)[d]			
None	134/436 (30.7)	121/431 (28.1)	[Reference]
1	23/436 (5.3)	28/431 (6.5)	−4.1 (−12.5 to 4.2)[c]
2	259/436 (59.4)	269/431 (62.4)	−3.1 (−9.6 to 3.6)[c]
3	20/436 (4.6)	13/431 (3.0)	3.3 (−4.0 to 10.6)[c]
Mode of respiratory support at time of BPD assessment (36 wk PMA), No./total (%)[b]			
None	112/436 (25.7)	105/436 (24.4)	[Reference]
Nasal high flow ≥2 L/min	159/436 (36.5)	145/436 (33.6)	0.7 (−7.8 to 9.1)[c]
CPAP or NIPPV	100/436 (22.9)	125/436 (29.0)	−7.2 (−16.5 to 2.1)[c]
Supplemental oxygen only	45/436 (10.3)	43/436 (10.0)	−0.4 (−10.6 to 9.8)[c]
Mechanical ventilation	20/436 (4.6)	13/436 (3.0)	4.1 (−4.2 to 12.5)[c]
Clinical BPD in survivors at 40 wk PMA (any supplemental oxygen or respiratory support), No. (%)	180/434 (41.5)	190/427 (44.5)	−3.0 (−9.6 to 3.6)[c]
Treatment with postnatal systemic corticosteroids for lung disease, No. (%)	174 (33.2)	176 (32.9)	0.3 (−5.4 to 6.0)[c]
Medications, No. (%)			
Vitamin A for BPD prophylaxis	9 (1.7)	11 (2.1)	−0.3 (−2.0 to 1.3)[c]
Bronchodilators	25 (4.8)	25 (4.7)	0.1 (−2.5 to 2.7)[c]
Diuretics for lung disease	112 (21.4)	106 (19.8)	1.6 (−3.5 to 6.6)[c]
Severe brain injury on cranial ultrasound: grade III or IV intraventricular hemorrhage and/or cystic periventricular leukomalacia, No./total (%)[e]	81/513 (15.8)	94/521 (18.0)	−2.3 (−6.8 to 2.3)[c]
Severe retinopathy of prematurity (stage ≥2) and/or treated with laser, cryotherapy, or intraocular therapy, No./total (%)[f]	244/437 (55.8)	235/434 (54.1)	1.7 (−4.9 to 8.3)[c]
Late-onset sepsis during hospital admission, No. (%)[g]	137 (26.1)	145 (27.1)	-1.0 (−6.2 to 4.3)[c]
NEC (modified Bell criteria stage ≥2), No. (%)[h]	42 (8.0)	43 (8.0)	−0.0 (−3.3 to 3.3)[c]
Patent ductus arteriosus treated with medication or surgical ligation, No. (%)	138 (26.3)	156 (29.2)	−2.8 (−8.2 to 2.6)[c]
Duration of mechanical ventilation via endotracheal tube, median (IQR), d[i]	8 (1-25)	8 (2-24)	0 (−3 to 2)[j]
Discharged home with oxygen or receiving supplemental oxygen in hospital after 52 wk PMA, No. (%)	146 (34.1)	142 (33.7)	0.4 (−6.0 to 6.7)[c]
PMA at cessation of any positive pressure respiratory support, median (IQR), wk[k]	37 (34-39)	37 (34-40)	0 (−1 to 1)[j]
PMA at cessation of supplemental oxygen, median (IQR), wk[l]	38 (32-42)	37 (32-42)	0 (−1 to 2)[j]
Length of hospital stay, median (IQR), d[m]	110 (90-133) [n = 427]	110 (94-135) [n = 421]	0 (−5 to 5)[j]

(continued)

survival free of BPD favored the budesonide and surfactant group. Results from ongoing trials will help to clarify if intratracheal budesonide therapy has any clinical utility. We did not observe any serious adverse effects from intratracheal budesonide administration.

The findings of this trial were consistent across prespecified clinical subgroups. We performed a post hoc subgroup analysis of infants with an F_{IO_2} of 0.50 or greater immediately prior to the first trial intervention, compared with those receiving a lower F_{IO_2}, in line with the inclusion criteria of the studies by Yeh et al.[16,17] There was some evidence that intratracheal budesonide may be beneficial in infants with a higher F_{IO_2}, but only 226 infants (21.3%) in this trial were in this subgroup, and only a minority of these infants survived without BPD, so caution is urged in interpreting this result.

Given the promising results of previous, smaller clinical trials of intratracheal budesonide, there was a need for larger trials to determine the efficacy and safety of intratracheal budesonide in both the short and longer terms. The largest previous trial by Yeh et al[16] found a more than one-third decrease

Table 2. Primary and Secondary In-Hospital Outcomes (continued)

Outcomes	Budesonide and surfactant (n = 524)	Surfactant only (n = 535)	Risk difference, % (95% CI)
z Scores at 36 wk PMA, mean (SD)			
Weight	−0.8 (1.2) [n = 426]	−0.9 (1.1) [n = 424]	0.1 (−0.1 to 0.2)[n]
Length	−2.3 (1.7) [n = 395]	−2.4 (1.6) [n = 395]	0.1 (−0.1 to 0.3)[n]
Head circumference	−1.1 (1.6) [n = 405]	−1.2 (1.4) [n = 410]	0.1 (−0.1 to 0.3)[n]
Body mass index	1.0 (1.2) [n = 393]	1.0 (1.2) [n = 394]	−0.0 (−0.2 to 0.1)[n]

Abbreviations: BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; PMA, postmenstrual age.

[a] BPD at 36 weeks' PMA was defined by 1 or more of the following criteria: (1) receiving mechanical ventilation, CPAP, NIPPV, or nasal high flow ≥2 L/min, regardless of the fraction of inspired oxygen (FIO_2); (2) effective FIO_2 ≥0.30 if receiving supplemental ambient oxygen or nasal prong flow <2 L/min to maintain target oxygen saturations; and (3) effective FIO_2 <0.30 if receiving supplemental ambient oxygen or nasal prong flow at <2 L/min to maintain target oxygen saturations *and* an unsuccessful air reduction trial.

[b] Adjusted for gestational age and mode of respiratory support at randomization, prior surfactant therapy (stratification variables), and clustering of infants within multiple pregnancy. Randomization was also stratified by study center, but this was not included in the model. See eTable 1 in Supplement 2 for unadjusted risk difference.

[c] Risk difference is unadjusted.

[d] BPD grade (severity) was defined according to the 2019 criteria of Jensen et al,[28] which are based on the type of respiratory support being received by an infant at 36 weeks' PMA, regardless of prior or current supplemental oxygen therapy: no BPD with no support; grade 1 BPD (least severe) with nasal cannula ≤2 L/min; grade 2 BPD with nasal cannula >2 L/min or noninvasive positive airway pressure; or grade 3 (most severe) BPD with invasive mechanical ventilation.

[e] There were 25 infants who did not have a cranial ultrasound performed.

[f] There were 188 infants who were not assessed for retinopathy of prematurity.

[g] Late-onset sepsis was defined as occurring after 48 hours of age with a positive bacterial or fungal culture from blood or cerebrospinal fluid, or a negative blood culture but clinical suspicion of sepsis and treatment with antibiotics/antifungals for ≥5 days.

[h] The modified Bell criteria[31] for necrotizing enterocolitis (NEC) grade the severity of NEC based on systemic and abdominal signs and radiological findings: stage I, suspected NEC; stage II, definite NEC requiring presence of pneumatosis or portal venous gas on abdominal radiograph; and stage III, advanced/severe NEC involving intestinal perforation and/or shock.

[i] There were 96 infants who did not receive mechanical ventilation for >2 hours, 45 in the budesonide and surfactant group and 51 in the surfactant-only group.

[j] Median difference (95% CI).

[k] Positive pressure support includes mechanical ventilation, CPAP, NIPPV, and nasal high flow ≥2 L/min.

[l] There were 5 infants who received no supplemental oxygen, 3 in the budesonide and surfactant group and 2 in the surfactant-only group.

[m] The denominator is infants who survived to hospital discharge.

[n] Mean difference (95% CI).

in the risk of the combined outcome of death or BPD with the use of intratracheal budesonide mixed with surfactant, compared with surfactant only, which would have been a revolutionary advance in the care of extremely preterm infants if confirmed. Infants randomized to receive budesonide in the current trial received the same dose as in the trial by Yeh et al[16] (0.25 mg/kg), with a higher mean cumulative dose (a mean of 1.7 doses [0.43 mg/kg] vs a mean of 1.4 doses [0.34 mg/kg]), but with first dosing at a somewhat later time (at a median age of 4 to 5 hours at randomization vs a mean age of 2 hours).

The strengths of the current trial include that it was conducted in 21 tertiary-level NICUs across 4 countries, strengthening external validity; was double-blinded; and was powered to find a clinically important difference in the absolute risk of survival free of BPD of at least 10%. The current trial enrolled one of the highest-risk (most immature) populations of extremely preterm infants ever included in a large randomized clinical trial. Compared with the study by Yeh et al,[16] the current trial enrolled a more immature and lower birthweight population of extremely preterm infants, with inclusion not only of infants receiving mechanical ventilation but also those receiving noninvasive respiratory support. This trial's participants could also have surfactant administered by any intratracheal technique.

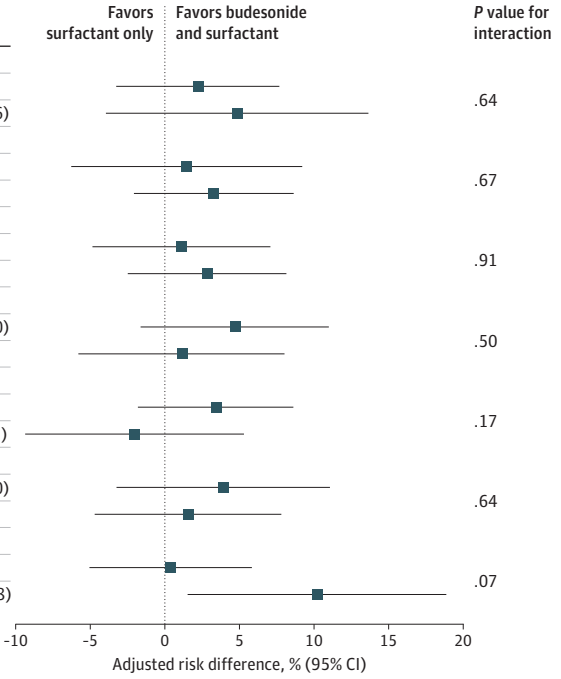
Limitations

This trial has several potential limitations. First, the sample size provided more than 90% power to detect an absolute increase in survival free of BPD of 10% from an estimated 50% in the control group to 60% (relative increase of 20%). However, the observed rate of survival without BPD in the surfactant-only group (22.6%) was lower than that predicted prior to the trial commencing. This would have augmented statistical power to detect an absolute increase of 10% in this outcome in the active treatment group, if present, but it would also have reduced statistical power to detect a relative increase of 20% (an absolute increase of 4.5%) in the outcome. The mean gestational age of 25.6 weeks and mean birth weight of 775 g among enrolled infants explains this lower-than-expected rate of the primary outcome compared with studies that enrolled more mature or heavier infants, including the trials by Yeh et al.[16,17]

Second, infants remained eligible for the trial even if they had previously been treated with surfactant; ultimately, more than half of enrolled infants had received surfactant prior to randomization. Given that it is not feasible to obtain antenatal or early postnatal consent for all extremely preterm births, we chose to include infants who had received prior surfactant to increase the generalizability of our results, and because this group of infants may still have benefited from intratracheal budesonide with subsequent surfactant therapy, particularly since they appeared to have more severe respiratory distress syndrome. Excluding such infants could have biased the study toward lower-risk infants. The inclusion of infants with prior surfactant would be of concern for external validity only if the prior surfactant substantially increased the incidence of survival free of BPD or it rendered the budesonide inactive, neither of which is likely. However, we acknowledge that if the intervention was used in routine

Figure 2. Percentage of Infants Alive and Free of Bronchopulmonary Dysplasia at 36 Weeks' Postmenstrual Age by Subgroup

Subgroup	No./total No. (%) Budesonide and surfactant	Surfactant only	Adjusted risk difference, % (95% CI)	*P* value for interaction
Gestational age				
22 wk 0 d to 25 wk 6 d	45/299 (15.1)	40/304 (13.2)	2.2 (−3.3 to 7.7)	.64
26 wk 0 d to 27 wk 6 d	89/225 (39.6)	81/231 (35.1)	4.8 (−4.0 to 13.6)	
Surfactant therapy				
No	67/229 (29.3)	61/229 (26.6)	1.5 (−6.3 to 9.2)	.67
Yes	67/295 (22.7)	60/306 (19.6)	3.3 (−2.1 to 8.6)	
Respiratory support at randomization				
Noninvasive	45/133 (33.8)	43/135 (31.9)	1.1 (−4.9 to 7.1)	.91
Invasive	89/391 (22.8)	78/400 (19.5)	2.8 (−2.5 to 8.1)	
Chorioamnionitis (clinical and/or histological)				
No	74/286 (25.9)	57/288 (19.8)	4.7 (−1.6 to 11.0)	.50
Yes	60/237 (25.3)	64/247 (25.9)	1.1 (−5.8 to 8.0)	
Small for gestational age				
No	131/451 (29.0)	116/461 (25.2)	3.4 (−1.8 to 8.6)	.17
Yes	3/73 (4.1)	5/74 (6.8)	−2.0 (−9.4 to 5.3)	
Sex				
Female	64/236 (27.1)	54/237 (22.8)	3.9 (−3.3 to 11.0)	.64
Male	70/288 (24.3)	67/298 (22.5)	1.5 (−4.7 to 7.8)	
FIO_2 prior to randomization[a]				
<0.50	109/411 (26.5)	106/407 (26.0)	0.4 (−5.1 to 5.8)	.07
≥0.50	21/104 (20.2)	15/122 (12.3)	10.2 (1.5 to 18.8)	



Subgroup analyses are adjusted for the 3 strata variables except for subgroups that are the strata variables, which are adjusted only for the remaining strata variables. The small-for-gestational-age subgroup risk difference is unadjusted due to small numbers.

[a]Post hoc subgroup analysis.

Table 3. Adverse Events

Adverse events	No. (%) Budesonide and surfactant (n = 524)	Surfactant only (n = 535)	Risk difference, % (95% CI)[a]
Hyperglycemia >180 mg/dL and/or receiving insulin therapy <14 d after first intervention	340 (64.9)	331 (61.9)	3.0 (−2.7 to 8.8)
Late-onset sepsis <14 d after first intervention[b]	75 (14.3)	80 (15.0)	−0.6 (−4.8 to 3.5)
Pulmonary hemorrhage <48 h after first intervention[c]	38 (7.3)	56 (10.5)	−3.2 (−6.5 to 0.0)
Pneumothorax requiring drainage	29 (5.5)	30 (5.6)	−0.1 (−2.8 to 2.7)
Spontaneous intestinal perforation[d]	19 (3.6)	17 (3.2)	0.4 (−1.7 to 2.6)
Gastrointestinal hemorrhage <14 d after first intervention[e]	15 (2.9)	20 (3.7)	−0.9 (−3.0 to 1.3)
Cardiopulmonary resuscitation and/or epinephrine within 24 h of intervention[d]	6 (1.1)	6 (1.1)	0.0 (−1.2 to 1.3)
Antihypertensive agents <14 d after first intervention	2 (0.4)	3 (0.6)	−0.2 (−1.0 to 0.6)
Oral candidiasis <14 d after first intervention	2 (0.4)	1 (0.2)	0.2 (−0.4 to 0.8)

SI conversion factor: To convert glucose to millimoles per liter, divide by 18.

[a] Effect estimates were adjusted only for clustering of infants within multiple pregnancy.

[b] Late onset sepsis was defined as occurring after 48 hours of age with a positive bacterial or fungal culture from blood or cerebrospinal fluid, or negative blood culture but clinical suspicion of sepsis and treatment with antibiotics/antifungals for ≥5 days.

[c] Pulmonary hemorrhage was a clinical diagnosis.

[d] Classified as a serious adverse event in the trial (along with death).

[e] Gastrointestinal hemorrhage was defined as fresh blood aspirated from an indwelling gastric tube.

clinical practice, it would usually be coadministered with the first dose of surfactant. The ongoing Budesonide in Babies trial (NCT04545866) enrolling at centers in the United States is including only extremely preterm infants who have not received prior surfactant, with prospective informed consent, and the results of that trial will be important in answering this question.

Third, the dose of budesonide was based on previous preclinical and clinical trials that reported benefit, but it is possible that the individual doses or cumulative dose of budesonide

were insufficient to achieve a therapeutic effect in the high-risk population studied. However, some research has suggested that the doses used are more than enough to exert a local glucocorticoid action.[32] The timing of the intervention (at a median age of 4 hours in the budesonide and surfactant group) may have also been too late; it is possible that budesonide would have a greater effect if given earlier (perhaps in the delivery room). Against this possibility, the subgroup of infants who had not received prior surfactant were enrolled at a median age of 1 hour (eTable 2 in Supplement 2), and intratracheal budesonide did not improve the primary outcome in this subgroup.

Conclusions

In extremely preterm infants with respiratory distress syndrome receiving surfactant, early intratracheal budesonide may have little to no effect on the risk of survival free of BPD at 36 weeks' PMA. Longer-term outcomes of the current trial at 2 years, as well as the results of other similar large randomized clinical trials will be important to fully characterize the effectiveness and safety of intratracheal budesonide and determine its role in clinical practice.

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