INHALED CORTICOSTEROIDS IN TRANSIENT TACHYPNEA OF THE NEWBORN (TTN): A RANDOMIZED, PLACEBO-CONTROLLED PILOT STUDY

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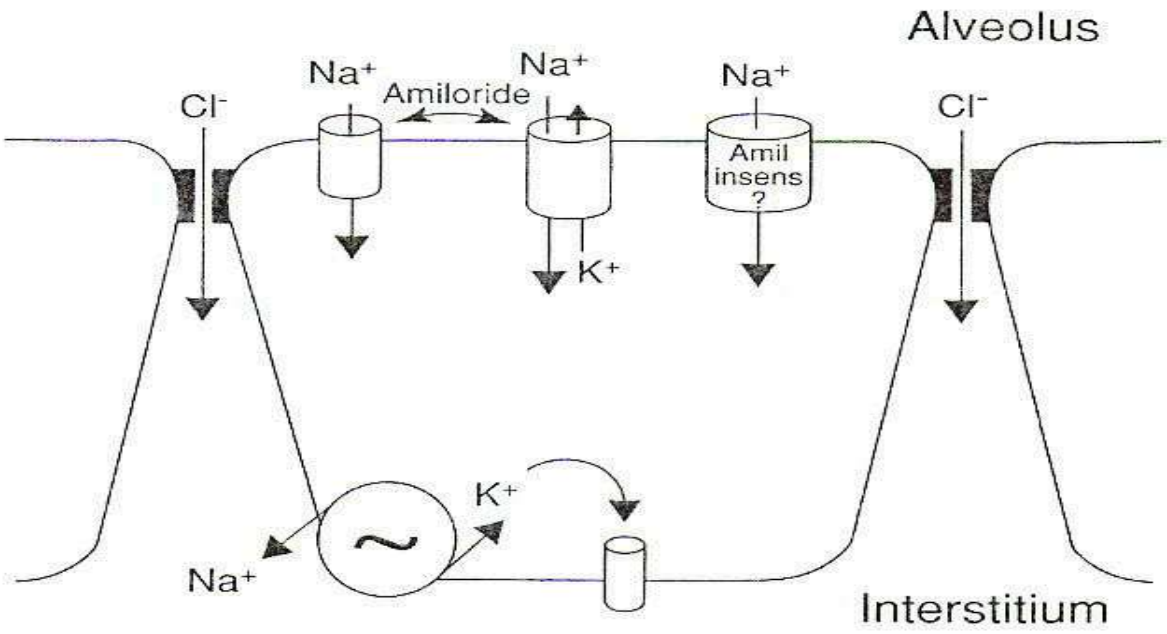
INTRODUCTION

- Studies suggest lower expression of ENAC subunits as a possible causative mechanisms for late preterm and term infants suffering from TTN (Walters DV et al, Pediatr Res 1978; Hummler E et al, Nat Genet 1996; Gowen CW et al, J Pediatr 1988).



INTRODUCTION

- Steroids
  - Increase transcription of ENAC in lung epithelia,
  - Decrease rate of degradation,
  - Increase the activity of the existing channels (Jain L et al, Am J Physiol. 1997)

- This led to clinical trials that explored the role of steroids in preventing TTN.

INTRODUCTION

Three large studies explored respiratory outcome of prenatal steroids in infants:

1. In term infants, antenatal steroids did not reduce the incidence of TTN but reduced the incidence of admission to the NICU with respiratory distress (Stutchfield P et al, BMJ 2005).

2. In late preterm infants, antenatal steroids did not lower the rate of either RDS nor TTN and did not affect the ventilator support (Porto AM et al, BMJ 2011).

3. In late preterm infants, prenatal steroids decreased neonatal composite of respiratory treatment, stillbirth or neonatal death (Gyamfi-Bannerman C et al, NEJM 2016)

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ORIGINAL ARTICLE

Antenatal Betamethasone for Women at Risk for Late Preterm Delivery

C. Gyamfi-Bannerman, E.A. Thom, S.C. Blackwell, A.T.N. Tita, U.M. Reddy, G.R. Saade, D.J. Rouse, D.S. McKenna, E.A.S. Clark, J.M. Thorp, Jr., E.K. Chien, A.M. Peaceman, R.S. Gibbs, G.K. Swamy, M.E. Norton, B.M. Casey, S.N. Caritis, J.E. Tolosa, Y. Sorokin, J.P. VanDorsten, and L. Jain, for the NICHD Maternal–Fetal Medicine Units Network*

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Betamethasone (N=1429)	Placebo (N=1402)
Indication for trial entry — no. (%)		
Preterm labor with intact membranes	400 (28.0)	392 (28.0)
Ruptured membranes	316 (22.1)	304 (21.7)
Expected delivery for gestational hypertension or preeclampsia	370 (25.9)	385 (27.5)
Expected delivery for fetal growth restriction	46 (3.2)	48 (3.4)
Expected delivery for oligohydramnios	50 (3.5)	42 (3.0)
Expected delivery for other indication	247 (17.3)	231 (16.5)
Gestational age at trial entry — no. (%)		
≤34 wk 6 days	369 (25.8)	399 (28.5)
35 wk 0 days to 35 wk 6 days	571 (40.0)	532 (37.9)
≥36 wk 0 days	489 (34.2)	471 (33.6)
Mean (±SD) maternal age — yr	28.6±6.3	27.8±6.1
Race or ethnic group — no. (%)†		
Black	376 (26.3)	381 (27.2)
White	828 (57.9)	800 (57.1)
Asian	57 (4.0)	39 (2.8)
Other, unknown, or more than one race	168 (11.8)	182 (13.0)
Hispanic	405 (28.3)	448 (32.0)
Nulliparous — no. (%)	457 (32.0)	448 (32.0)
Smoking during current pregnancy — no. (%)	204 (14.3)	186 (13.3)
Preeclampsia or gestational hypertension — no. (%)	433 (30.3)	440 (31.4)
Gestational diabetes — no. (%)	153 (10.7)	153 (10.9)
Major congenital anomaly in infant — no. (%)‡	11 (0.8)	21 (1.5)

* There were no significant differences between the two groups except for maternal age (P=0.001) and Hispanic ethnic group (P=0.03).
† Race or ethnic group was self-reported. Patients of any race could report Hispanic background.
‡ Although the presence of a major congenital anomaly was an exclusion criterion, these disorders were not discovered until birth.

Primary outcome: the composite of treatment in the first 72 hours (the use of continuous positive airway pressure or high-flow nasal cannula for at least 2 hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least 4 hours, extracorporeal membrane oxygenation, or mechanical ventilation) or stillbirth or neonatal death within 72 hours after delivery.

Table 2. Neonatal Respiratory Outcomes.*

Outcome	Betamethasone (N=1427)	Placebo (N=1400)	Relative Risk (95% CI)	P Value
	no. (%)			
Primary outcome†	165 (11.6)	202 (14.4)	0.80 (0.66–0.97)	0.02
CPAP or high-flow nasal cannula for ≥2 continuous hr	145 (10.2)	184 (13.1)	0.77 (0.63–0.95)	0.01
Fraction of inspired oxygen of ≥0.30 for ≥4 continuous hr	48 (3.4)	61 (4.4)	0.77 (0.53–1.12)	0.17
Mechanical ventilation	34 (2.4)	43 (3.1)	0.78 (0.50–1.21)	0.26
ECMO	0	0	NA	NA
Stillbirth or neonatal death ≤72 hr after birth	0	0	NA	NA
Severe respiratory complication‡	115 (8.1)	169 (12.1)	0.67 (0.53–0.84)	<0.001
CPAP or high-flow nasal cannula for ≥12 continuous hr	93 (6.5)	147 (10.5)	0.62 (0.48–0.80)	<0.001
Fraction of inspired oxygen of ≥0.30 for ≥24 continuous hr	20 (1.4)	34 (2.4)	0.58 (0.33–1.00)	0.05
Need for resuscitation at birth§	206 (14.5)	260 (18.7)	0.78 (0.66–0.92)	0.003
Respiratory distress syndrome	79 (5.5)	89 (6.4)	0.87 (0.65–1.17)	0.36
Transient tachypnea of the newborn	95 (6.7)	138 (9.9)	0.68 (0.53–0.87)	0.002
Apnea	33 (2.3)	37 (2.6)	0.88 (0.55–1.39)	0.57
Bronchopulmonary dysplasia	2 (0.1)	9 (0.6)	0.22 (0.02–0.92)¶	0.04
Pneumonia	6 (0.4)	13 (0.9)	0.45 (0.17–1.19)	0.10
Surfactant use	26 (1.8)	43 (3.1)	0.59 (0.37–0.96)	0.03
Composite of respiratory distress syndrome, transient tachypnea of the newborn, or apnea	198 (13.9)	249 (17.8)	0.78 (0.66–0.93)	0.004
Pulmonary air leak	5 (0.4)	6 (0.4)	0.82 (0.25–2.68)	0.74

INTRODUCTION

- There are limited postnatal treatments for TTN
- The administration of a single dose of inhaled B_2 agonists effectively reduced respiratory morbidity in late preterm and term infants with TTN (Armangil D et al, J Pediatr 2011),
  - Glucocorticoids may enhance that effect (Jobe AH et al, Biol Neonate 1997)
  - <u>β-agonists in TTN</u>
  - Rationale: β-agonists can accelerate the rate of alveolar fluid clearance.
  - At present there is insufficient evidence to determine the efficacy and safety of β-agonists in the management of TTN.
  - The quality of evidence was low (Moresco L et al, Cochrane 2016)

STUDY AIM

- To determine if early inhaled corticosteroids could alleviate the respiratory distress and morbidity in late preterm and term neonates with TTN

METHODS: STUDY DESIGN

- This was a randomized, double blind placebo controlled, multicenter pilot study, conducted at three university affiliated NICUs in Israel between March 2012 and June 2016
- The study was approved by the ethics committee of the Israeli Ministry of Health and by the institutional review board in each center
- Parents of all infants signed an informed consent form

METHODS: PATIENTS INCLUSION CRITERIA

1. Infants post-menstrual age ≥ 34 weeks delivered by cesarean section or vaginal delivery
2. Diagnosis of TTN consistent with:
   A. Onset of tachypnea (RR ≥ 60 breaths/min) within 6 hours after birth and need for FiO_2 ≥0.25 (Armangil D et el, J Pediatr 2011; Riskin A et al, Am J Perinatol 2005)
   B. Tachypnea persisting for at least 4 hours (Porto AM et al, BMJ 2011; Armangil D et el, J Pediatr 2011)
   C. Chest radiograph - prominent central vascular markings, widened interlobar fissures with pleural fluid, symmetrical perihilar congestion
   D. The symptoms and radiographic findings were transient and self-limited, disappearing within the first week of life (usually even within the first three to 4 days)

METHODS: PATIENTS EXCLUSION CRITERIA

1. Meconium aspiration syndrome
2. Respiratory distress syndrome
3. Congenital heart disease
4. Non respiratory disorders causing tachypnea (polycytemia or hypoglycemia) resolving with treatment of the disorder
5. Pneumonia by chest x-ray
6. Suspected sepsis/bacteremia
7. Prenatal steroids

METHODS: STUDY PROCEDURE

- Eligible infants were randomized to 2 doses of
  - Placebo (0.9% normal saline solution 2 ml)
  - Inhaled corticosteroids (Budesonide 2 ml=1000 mcg)

  - The first dose was given at the time of enrollment, within 6 hours of age, and the second dose 12 hours later

METHODS: STUDY PROCEDURE

- Assessment before the first dose of inhaled study medication included:
  1. Clinical: RR, HR, blood-pressure, FiO_2, TTN clinical score and respiratory support level
  2. Laboratory: CBC, I/T ratio, glucose and venous blood gas
  3. Chest x-ray

- Clinical assessment - every 2 hours during the first 48 hours or until the resolution of respiratory distress by the nursing team

- Repeat clinical score - after 12, 24 and 48 hours from study entry by the treating physician

METHODS: STUDY PROCEDURE

Table 1: TTN Clinical Score

	0	1	2
Grunting	No	Intermittent	Continuous
Retractions	No	Intermittent	Continuous
Ala nasi	No	Intermittent	Continuous
Respiratory rate (breaths/minute)	<60	60-100	>100

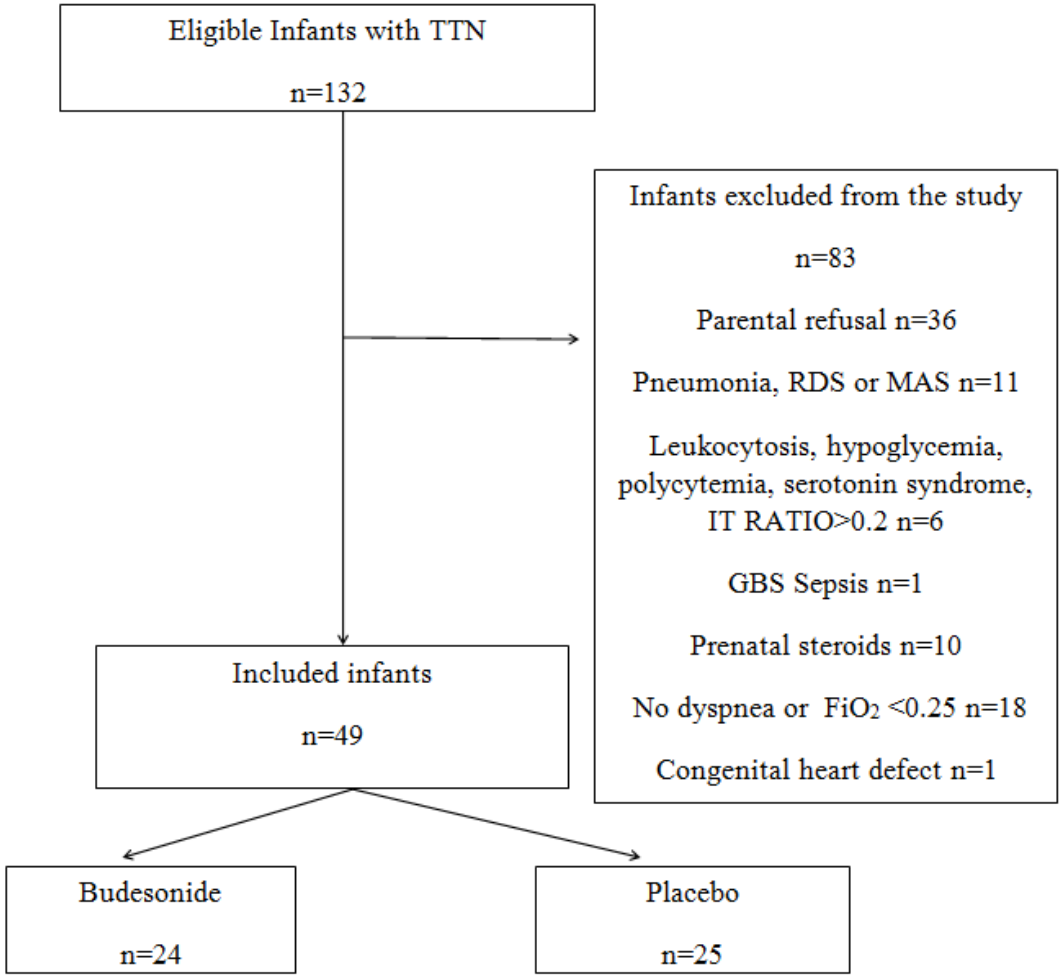
*Scoring of clinical status of the newborn (Armangil D et el, J Pediatr 2011)

METHODS: STUDY PROCEDURE

- The primary outcome measure was the assessment of respiratory distress reflected by TTN clinical score, respiratory support and FiO_2 at 12, 24 and 48 hours after the first dose of inhaled study medication
- The secondary outcome was the assessment of morbidity associated with TTN
- Sample size was calculated to detect a difference of two points (25%) in the change of mean TTN clinical score before and after treatment. Sample size calculation for two-tailed t-test was 25 infants in each group. Alpha of 0.05 with power of 80%
- Analysis was done by intention to treat

RESULTS

INFANTS ENROLLMENT



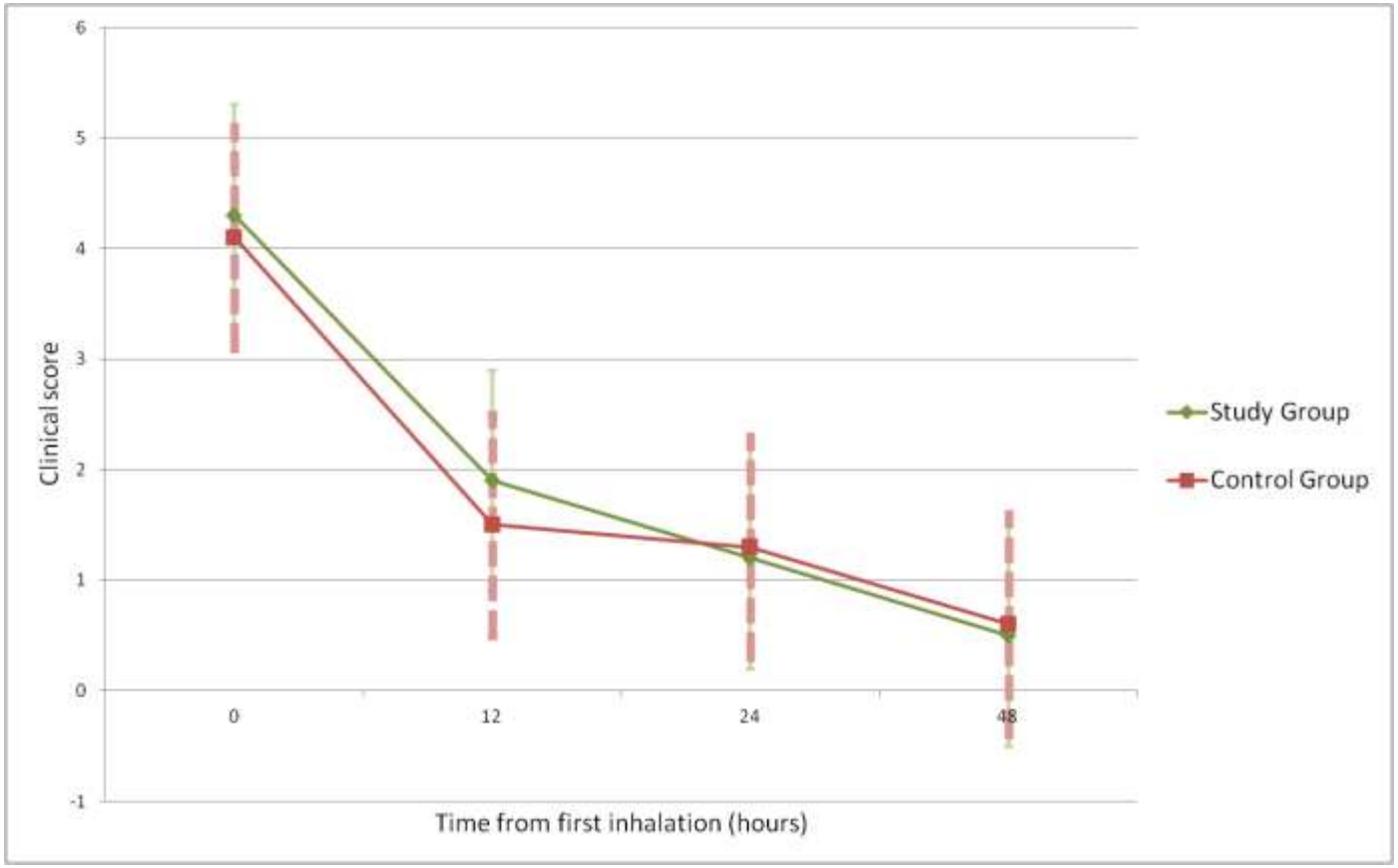
INFANTS' CHARACTERISTICS

	Budicort n=24	Placebo n=25	p value
Gestational age (weeks)	36.8±1.9	36.4±1.8	0.45
Birth weight (g)	2986±660	2715±515	0.11
Apgar 5 minutes	9.2± 0.8	9.2±0.7	0.89
Maternal age (year)	33.6±5	30.6±5.6	0.05
ROM (hr)	5.1±10.1	29±127	0.35
Male	20 (83%)	17 (68%)	0.36
Singleton	21 (87%)	21 (84%)	0.44
Cesarean section	12 (50%)	12 (48%)	0.27
Maternal diabetes or GDM	6 (25%)	2 (8%)	0.24
Maternal GBS	2 (8%)	1 (4%)	0.57
Peripartum ABX	5 (21%)	6 (24%)	0.97

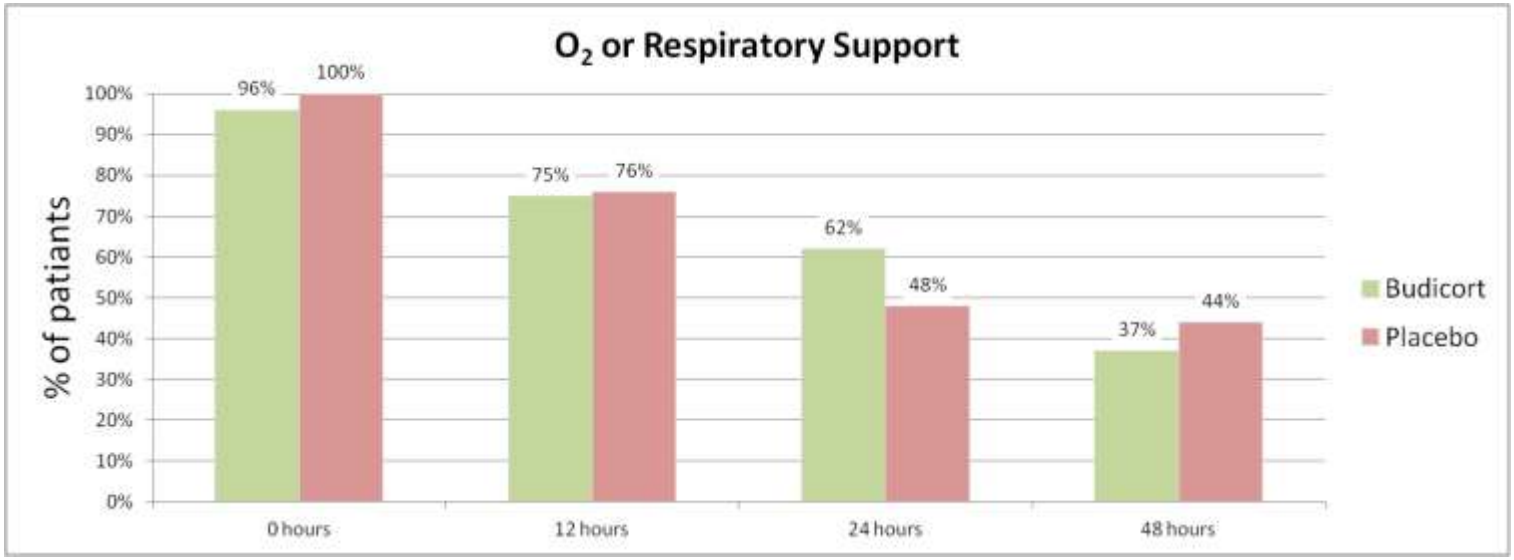
INFANTS' CHARACTERISTICS

Recruitment data:	Budicort	Placebo	
Age (hours)	6.25±2.8	6.28±2.5	0.91
RR (breath/min)	73.6±27.3	77.5±24.8	0.60
HR (beats/min)	140±19.1	135.2±20.2	0.40
MBP (mmHg)	43.1±6.3	42.8±5.9	0.88
SpO_2 (%)	95.7±3.7	96.9±3.5	0.27
FiO_2	0.30±0.10	0.29±0.10	0.48
TTN Clinical Score	4.3±1.6	4.1±2.1	0.42
Hct (%)	51.4±7.1	52.1±7.9	0.75
WBC (X 10^9 cells/L)	14.8±5.1	14.1±5.2	0.59
I/T ratio	0.10±0.04	0.02±0.5	0.04
Glucose (mg/dL)	69.4±22.4	75.7±14.6	0.25
pH	7.29±0.00	7.30±0.10	0.43
$PvCO_2$	48.2±6.5	50.3±9.9	0.39
O_2 or respiratory support	23 (96%)	25 (100%)	1.00

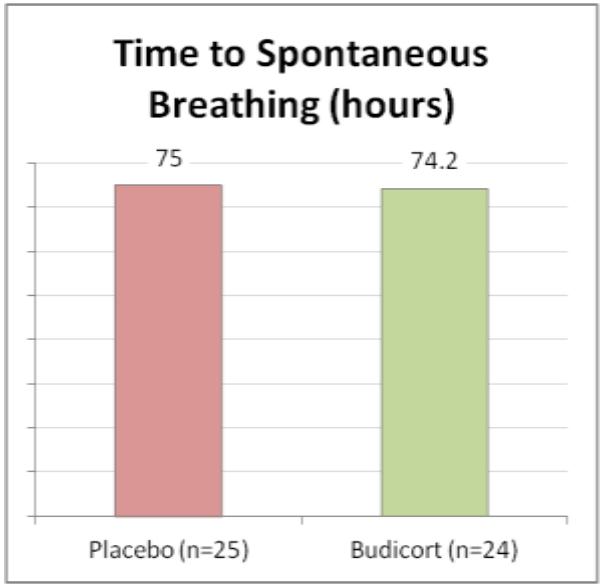
CLINICAL PRIMARY OUTCOME

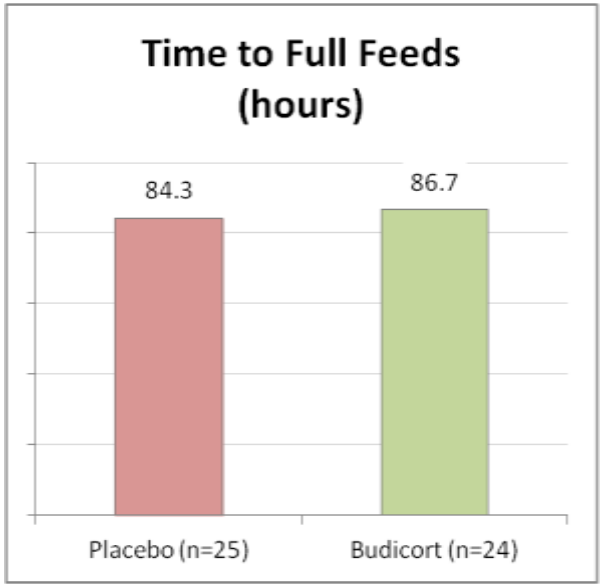


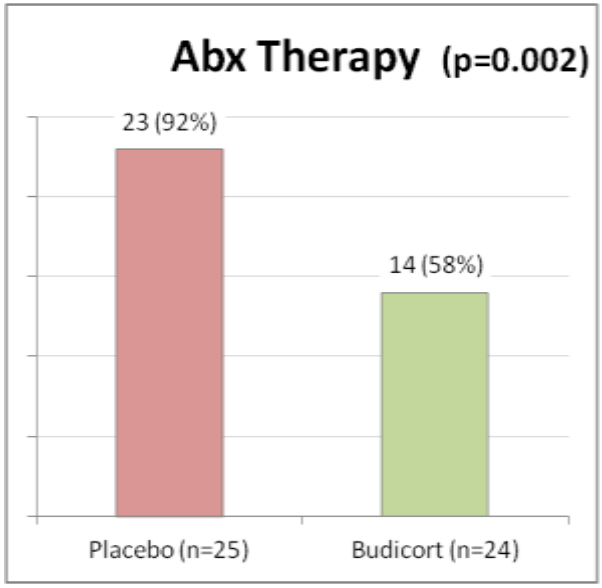
CLINICAL PRIMARY OUTCOME

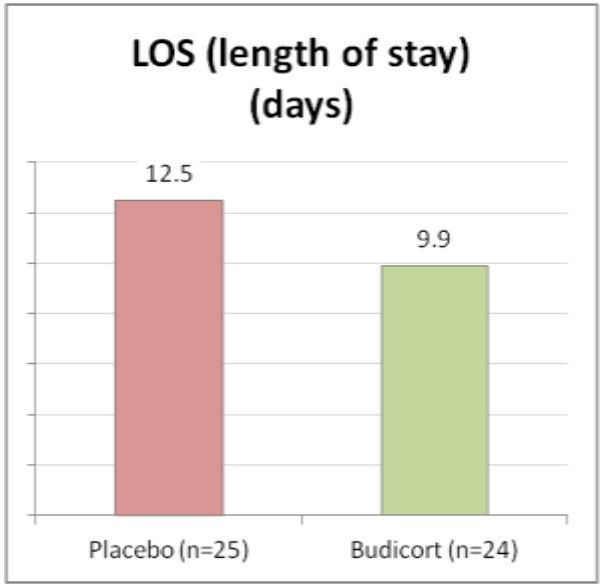


SECONDARY OUTCOME



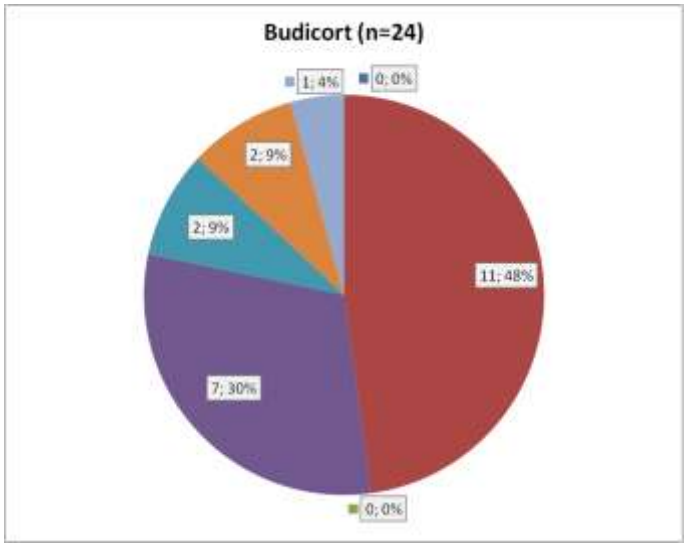


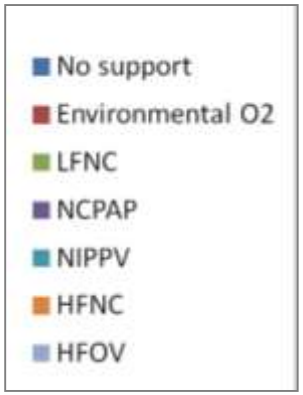


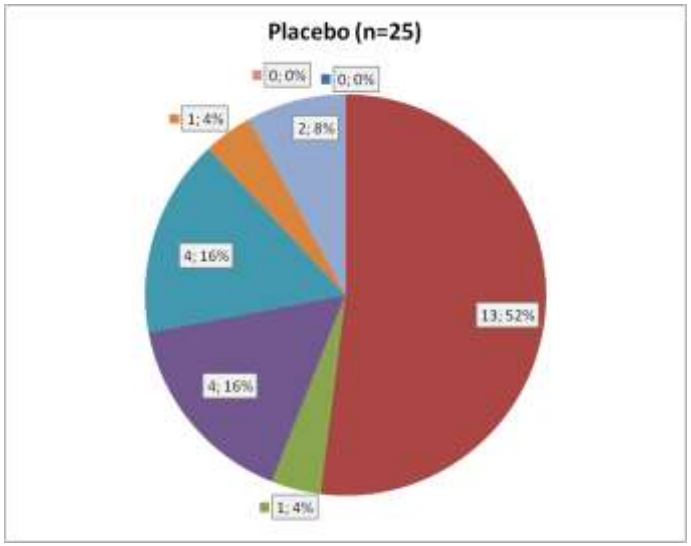


SECONDARY OUTCOME

Maximal Respiratory Support:







DISCUSSION

- The inhaled steroids did not affect the primary outcome (respiratory status) or the secondary outcomes in our study at any time point within the first 48 hours of life

- The only significant difference was in the rate of antibiotic therapy, being higher in the control group, though length of therapy was comparable between the groups

DISCUSSION

- Explanation for the negative results of our pilot study:

1. The effect of steroids is not immediate; better for prevention
2. The treatment was inhaled with limited lung deposition
3. Type II error; Yet, we did not observe even a trend of such a benefit
4. The study included late preterm but also term infants as opposed to the study of Gyamfi-Bannerman that included only infants at 34-6 weeks gestation (sub analysis only on the late preterm infants was consistent with no effect)

STUDY STRENGTH

- Design - randomized, double-blind control multicenter study
- Novelty - first study that examined the effect of early inhaled corticosteroids in the treatment of TTN
- Clinical significance:
  - Applicable to a common clinical condition
  - Targeting the population at most need and not all mothers

STUDY LIMITATIONS

- Small sample size – possible type II error
- No analysis of lung deposition of the inhaled steroids to avoid ethical issues and limited parental consent
- A larger dose of inhaled steroids or systemic dose should be considered in future studies
- The study was too small to assess safety for uncommon side effects

CONCLUSIONS

- This pilot study was unable to detect a significant effect of inhaled Budicort on the respiratory course of TTN in late preterm and term infants

- We detected no short term adverse outcomes

CLINICAL IMPLICATIONS

- Our study is important for future RCT design when planning the mode, dose and type of steroid treatment and in choosing the correct target population (preterm vs. term infants)

- A larger study might be needed in the future to confirm or rule out a beneficial effect of inhaled or systemic steroids in infants with TTN

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ORIGINAL ARTICLE: NEONATAL LUNG DISEASE

WILEY

Inhaled corticosteroids in transient tachypnea of the newborn: A randomized, placebo-controlled study

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THANK YOU FOR LISTENING!