Statistical Analysis Plan for the Doxie Trial

Protocol Title	Delayed Cord Clamping with Oxygen In Extremely Low Gestational Age Infants
Principal Investigator	Anup Katheria M.D.
Study Sites	• Sharp Mary Birch Hospital for Women & Newborns • University of California Davis Medical Center • University of California San Diego
Study Activation Date	November 17,2021
Planned Accrual	n=140
Planned Accrual Period	2 years
Planned Duration	5 years
Trial identifiers:	NCT04413097 1R03HD105224

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1a Protocol Summary

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Planned Accrual	n=140
Planned Accrual Period	2 years
Planned Duration	5 years
Study Design	Randomized controlled trial comparing the delivery of two oxygen concentration delivered by mask CPAP/PPV during 90 seconds of delayed cord clamping of premature infants born less than 29 weeks gestation
Study Objectives	To assess the feasibility and compare the incidence of preterm infants (up to 28+6 weeks GA) who achieve a peripheral oxygen saturation of 80 percent by 5 MOL given mask CPAP/PPV with an FiO2 of 1.0 during DCC for 90 seconds (HI Group) to infants given mask CPAP/PPV with an FiO2 of .30 during DCC for 90 seconds (LO Group).
Treatment Description	During 90 seconds of delayed cord clamping, the infant will receive gentle stimulation and start CPAP by 30 seconds of life at an FiO2 1.0 or 0.30 with CPAP of 5 cmH20. If the infant is apneic or there is no Pedicap color change the team will begin positive pressure ventilation (starting PIP of 20 cmH20) by 60 seconds of life. The infant will remain on this support up until the umbilical cord is clamped at 90 seconds of life. Once the cord is clamped the infant resuscitation will continue according to unit protocol.
Inclusion Criteria	• Premature infants born at 22-28+6 weeks gestation • Informed consent obtained (antenatal)
Exclusion Criteria	• Declined consent • Infants with known congenital anomalies • Bleeding Accreta/Maternal Hemorrhage

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	• Monochorionic multiples with evidence of TTTS • Fetal or maternal risk • Preterm Prolonged Rupture of Membranes prior to 20 weeks gestation • Parents request no resuscitation
Protocol Title	• Delayed Cord Clamping with Oxygen in Extremely Low Gestational Age Infants

Study Outcomes	Primary:
	To assess the feasibility and compare the incidence of preterm infants (up to 28+6 weeks GA) who achieve a peripheral oxygen saturation of 80 percent by 5 MOL given mask CPAP/PPV with an FiO2 of 1.0 during DCC for 90 seconds (HI Group) to infants given mask CPAP/PPV with an FiO2 of .30 during DCC for 90 seconds (LO Group).
	Secondary:
	• Time frame: study completion to discharge
	  ○ Incidence of Grade III and IV intraventricular hemorrhage
	  ○ Incidence of all grades of intraventricular hemorrhage
	• Time frame: First 10 minutes of life
	  ○ Resuscitation interventions
	  ○ Changes in heart rate (BPM)

2a Background and Rationale

Current delivery room practice is to delay clamping and cutting of the umbilical cord to allow for hemodynamic stabilization. Supported by numerous randomized controlled trials (1-10) and meta-analyses (11, 12), this practice is endorsed by neonatal and obstetrical governing bodies. (13-15) However, data are very limited in extremely low gestational age infants less than 29 weeks gestation at birth.

The timing of delayed cord clamping (DCC) requires careful consideration in infants born at less than 29 weeks gestation, due to their critical transition to lung aeration and gas exchange. Animal studies demonstrate that delaying umbilical cord clamping until after breathing is established can prevent adverse cerebral and cardiac hemodynamics, potentially reducing bleeding in the brain or severe intraventricular hemorrhage (sIVH). (16-19) In a multicenter trial comparing DCC to umbilical cord milking, 76 percent of 23+0 – 27+6 weeks gestation who received DCC without respiratory support had initiated breathing before cord clamping. (20) Despite most DCC infants beginning to breathe before cord clamping, relative hypoxemia was

common, as indicated by a low arterial oxygen saturation at 5-minute of life (SpO2, 73 percent (95% CI 71.4, 75.6)). (21) The significance of this observation is evident from two recent analyses establishing those preterm infants with a 5-minutes of life (MOL) SpO2 <80 percent were more likely to have sIVH or death. (22, 23)

To date, all studies of ventilation during DCC have used room air or low levels of oxygen (0.21-0.30) and have shown no reduction in morbidities. (24-26) Ventilation through a mask with low levels of oxygen may not be sufficient in improving the outcomes of extremely preterm infants. Additionally, non-invasive respiratory support during transition requires a patent airway, allowing air to enter the trachea and aerate the lung and spontaneous breathing is the most effective method of opening the airway for a newborn. However, hypoxia inhibits breathing movements and contributes to a closed glottis (27), which prevents lung aeration and subsequent benefits of DCC.

Historically, efforts to reduce early hypoxia has led to high oxygen concentrations being used during resuscitation of very preterm infant and has been associated with death or organ injury. (28, 29) A recent trial demonstrated that stabilization with a brief period of 100 percent oxygen post-delivery led to greater minute ventilation, higher tidal volumes, and improved oxygenation compared to 30 percent oxygen. (27) Despite this data, several multicenter trials of resuscitation with intact umbilical cord start with low oxygen levels and many require 3-5 minutes to establish breathing during DCC (30-33). To test feasibility and safety, 100 percent oxygen was administered to seven preterm infants during 60 seconds of DCC. All infants who received continuous positive airway pressure (CPAP) and 100 percent oxygen at birth achieved a saturation above 80 percent by 5 MOL, and all survived without sIVH. A higher alveolar oxygen tension may be critical to initial stabilization and oxygenation of the extremely preterm infant. Preliminary animal work suggests 100 percent oxygen during DCC provides an optimal increase in pulmonary blood flow without a large increase partial pressure of oxygen (PaO2), due to the simultaneous streaming of umbilical venous blood with relatively low PaO2. A pilot study with detailed assessments of hemodynamics and organ function immediately after birth is needed to determine the efficacy and safety of providing 100 percent oxygen during DCC.

3a Primary objective:

- To assess the feasibility of providing mask CPAP/PPV with an FiO2 of 0.30 or 1.0 during DCC for 90 seconds.

4a Primary outcome

The primary efficacy outcomes of this study is the achievement of peripheral oxygen saturation of 80 percent by 5 minutes of life. Defined as maintaining a peripheral oxygen saturation of 80 percent before the 5th minutes of life.

5a Secondary outcome:

- Any Intraventricular Hemorrhage (grades 1-4)

    - Time Frame: Through study completion at hospital discharge, up to 6 months corrected gestational age (CGA)
- Intraventricular hemorrhages (grades 3-4) (bleeding in the brain parenchyma and/or ventricular dilation on either side of the brain)
    - Time Frame: Through study completion at hospital discharge, up to 6 months corrected gestational age (CGA)
    - Assessed by intracranial ultrasound or MRI.
- Resuscitation interventions including intubation, chest compressions, medications received before admission to NICU.
    - Time Frame: In the first 10 minutes of life.

6a Safety/harms

Due to the small size of this pilot project, there will be no interim analyses and formal stopping rules have not been established. The Medical Monitor will review Serious Adverse Events as they occur and will request specific data for analysis from the Data Manager and/or Statistician when/if they feel there is a safety signal occurring.

The population being studied is at an increased risk of all complications associated with prematurity. The majority of these events will be expected and included in data collection and reported in the final analysis. However, SAE of death and severe IVH will be reported to the Data Manager and Medical Monitor within 72 hours of discovery.

6b Expected Adverse Events

Captured in data collection and reported in final analyses.

- Intraventricular hemorrhages grades 1-2.
    - Defined as bleeding in the brain parenchyma and/or ventricular dilation on either side of the brain)
- Severe Retinopathy of Prematurity
- Chronic Lung Disease (mode of respiratory support at 36 weeks' post-menstrual age as defined and categorized by: Jensen, Dysart, Gantz, et al: Defining bronchopulmonary dysplasia) http://www.ncbi.nlm.nih.gov/pmc/articles/pmc6775872/
- Necrotizing enterocolitis (Bell's stage >2)
- Spontaneous intestinal perforation

6c Serious Events

All SAEs of death and severe IVH will be entered into the electronic data acquisition system and reported to the DM within 72 hours of discovery of event. The Data Manager will forward all SAE death and severe IVH reports to the Medical Manager and Primary Investigator.

- Any Serious Unexpected Problem (UP) or Serious Deviation will be entered into the electronic data acquisition system within 7 days of discovery of event. The Data Manager will forward all unexpected SAE reports to the Medical Monitor and Principal Investigator.

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6d Data Monitoring

A data safety monitoring board (DSMB) will be established to: 1) protect all study patients, 2) safeguard the interests of all study patients, 3) monitor the overall conduct of the trial, 4) advise the investigators to protect the integrity of the trial. The DSMB will receive reports from the trial on any injuries or adverse events, any developments that jeopardize the continued success of the trial. The data coordinating center will inform the DSMB of all expected and unexpected adverse events. Recommendations from the DSMB will be addressed to the study's principal investigator.

It will be the responsibility of the trial investigators to notify the IRB of record involved of any issues that are relative to patient safety or to early stopping of the study. The electronic data entry system will automatically notify all appropriate individuals once an SAE is entered into the database.

7a Trial design

This randomized double-blinded pilot trial of infants (up to 28+6 weeks GA). A total of 140 infants will be randomized to receive continuous positive airway pressure (CPAP) and/or positive pressure ventilation (PPV) by face mask with an inspired fractional oxygen (FiO_2) of 1.0 (HI Group) or FiO_2 of 0.30 during 90 seconds of DCC (LO Group). Randomization will be stratified by birth gestational age groups (22+0 – 25+6 vs 26+0 – 28+6). Stratification will be blocked in groups of four to allow for an equal distribution of infants between the two stratification groups. Multiples will be included and randomized individually. After intact cord resuscitation is complete using the randomly assigned FiO_2 settings the cord is clamped at 90 seconds or earlier at the discretion of the clinical team. Subsequently the infant is resuscitated as per unit protocol (i.e., CPAP/PPV with a starting FiO_2 0.30).

7b Inclusion criteria

1. Inborn infants of either gender or any race with best obstetrical estimate of gestation <29 weeks.
2. Single and Multiple pregnancy
3. All modes of delivery (vaginally or cesarean section)
4. Informed consent signed and dated by parent and/or guardian prior to delivery.

7c Exclusion criteria

1. Parents decline consent.
2. Congenital anomalies of the newborn.
3. Bleeding Accreta.
4. Monochorionic multiples with evidence of TTTS.
5. Fetal or maternal risk identified by obstetric or neonatal clinician.
6. Preterm premature rupture of membranes prior to 20 weeks gestation.
7. Parents request no resuscitation.

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8a Intervention

8b Randomization

Randomization will be performed at the overall study level and stratified by gestational age (22+0 – 25+6 vs 26+0 – 28+6). At the time of cesarean section or during labor each participating infant will be randomly assigned to receive either a low oxygen concentration (FiO2 .30) or a high oxygen concentration (FiO2 1.0) during 90 seconds of delayed cord clamping. The research team member will open a randomization card when notified of a subject's impending birth, review the protocol with the obstetric provider performing the procedure, set-up the sterile stabilization bed. The research team member will set the oxygen blender as indicated by the randomization card and cover the blender to blind the FiO2 setting.

At delivery, the infant will be placed on a stabilization bed or on the mother's abdomen that allows the infant to be close to the mother and the umbilical cord to remain intact for eDCC. If the infant is resuscitated on the mother's abdomen a separate resuscitation stand will be used.

- If an infant is randomized to DCC and Low Oxygen concentration (DCC LO group), the following procedure will ensue:
  - During delayed cord clamping, the infant will be gently stimulated by drying the infant with a sterile towel and provide CPAP by 30 seconds of life. During delayed cord clamping, breathing assistance with CPAP of 5 cmH20 and a FiO2 0.3 will be provided.

- If an infant is randomized to DCC and High Oxygen concentration (DCC HI group), the following procedure will ensue:
  - During delayed cord clamping, the infant will be gently stimulated by drying the infant with a sterile towel and provide CPAP by 30 seconds of life. During delayed cord clamping, breathing assistance with CPAP of 5 cmH20 and a FiO2 1.0 will be provided.

Patency of the airway will be assessed by a Colorimetric CO2 detector. If there is no color change on the Colorimetric CO2 detector, the neonatal provider will reposition and reattempt to open the airway, if there is no improvement, PPV will be initiated by 60 seconds of life (staring with 20 cmH2O). Cord clamping will occur no earlier than 90 seconds of life and the infant will be transferred to a standard neonatal warmer and resuscitated per NRP guidelines.

8c Protocol Deviations

All clinical staff involved with implementing the intervention will receive training in protocol adherence and safety measures. Neonatal providers will be in sterile gown during the procedure and use non-sterile masks for ventilation. Every effort will be made to avoid touching any parts of the sterile field while the provider is administering CPAP/PPV. Umbilical cord milking is prohibited in this proposed group (<29 weeks).

8d Masking

Randomization and intervention will remain blinded to the participant’s clinical care team during the entire study period. The research team member conducting the randomization will not be involved in the clinical care of the infant.

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9a Masked Data Review for Adjudication

To address potential errors in coding the primary outcome, which may arise because the research enrollment forms are completed during the time of resuscitation an adjudication process will be implemented. Errors will be minimized by having the study coordinators review the documentation of each enrollment. The specified SpO_2 goals status will be evaluated through an adjudication process conducted after enrollment for the study is complete. The adjudication process will be conducted for participants surviving to 5 minutes by each site's principal investigator to ensure accurate reporting of the final primary outcome status for publication. Site Principal Investigators blinded to randomization assignment review delivery room records and recorded the time infant reached a stable oxygen saturation of 80%.

9b. Adjudication criteria

- When available video, pulse oximetry and electrocardiogram data will be used to confirm saturation values in the first 5 minutes of life.

10a Statistical Methods

All aspects of data analysis and statistical investigations will be directed by Dr. Debra Poeltler, who has formal training in biostatistics and has expertise in multivariate data sets such as these.

Outcomes, morbidities and composite outcomes will be dichotomized (no/yes) and will each be initially compared between the HI and LO groups using chi-square testing. The occurrence of one or more of the composite outcomes will be considered an occurrence. Subsequent testing will utilize logistic regression to calculate odds ratios to evaluate the outcomes in the HI and LO groups after adjusting for variables found to be significant in univariable testing.

Data will be first verified for accurate data entry, formats, coding, and missing observations. The largest and smallest values for each variable will be reviewed for accuracy and plausibility. Each variable will be examined for variability and frequency distribution, skewness and kurtosis. A variety of graphical techniques will be used to display and assess data such as histograms, boxplots and scatterplots, etc. All significance tests will be two sided with a critical alpha level of 0.05. Data analyses will use SPSS (IBM Corp. Released 2016. Version 24.0. Armonk, NY) and R programming package (Version 4.0.0, the R Foundation for Statistical Computing, Vienna, Austria 2020-04-24).

11a Primary Analysis

11b Primary Outcome

An adjudicated primary outcome determining whether is participant met or failed to meet the primary outcome will be used in conducting the primary analysis for the overall study. Linear regression will be used to evaluate the differences in 5-minute saturations between the HI and LO groups and the relationship with breathing prior to cord clamping (dichotomized no/yes) and development of severe IVH/death. It is not anticipated that data will be missing for the primary outcome as in addition to research study documentation vitals are routinely collected by the clinical team at five minutes of life.

SpO2 values will be converted to dichotomous outcome (sat >80% at 5 MOL, no/yes)

and chi-square testing will be used to evaluate the difference between the HI and LO groups. Analyses will be conducted by coding the high oxygen group as 1 and the low oxygen group as 0. Chi-square testing will be used to evaluate the difference between the two randomization groups. Subsequent analyses will use logistic regression to estimate odds ratios (95% CI) for SpO2 < 80% by 5 MOL (no/yes) between the HI and LO groups after adjusting for other delivery room/maternal variables found to be significant in univariable testing.

11c Secondary Outcomes

Linear regression will be used to evaluate the differences in 5-minute saturations between the HI and LO groups and the relationship with breathing prior to cord clamping (dichotomized no/yes) and development of severe IVH/death. Longitudinal repeated measures modeling with GEE will be used to test the differences in each of the physiologic parameters SpO2, StO2, FiO2 and MAP over the first ten minutes between the HI and LO groups. Variables found to be significant in univariable testing with each of the parameters will be considered for inclusion in model fitting. Longitudinal repeated measures modeling with GEE will be used to test the differences over the first 24 hours for cerebral tissue oxygenation and blood pressure between the HI and LO groups. Variables found to be significant in univariable testing will be considered for inclusion in model fitting.

Similarly, the time to achieve a saturation of 80 percent will be compared using ROC curves and AUC measurements should both groups no longer have a different saturation at 5 minutes.

Measures of systemic and cerebral blood flow will be compared using appropriate tests for normally distributed values means (T-tests).

Neonatal care during delayed cord clamping variables to be summarized will include assignment of correct FiO2, time to cord clamping, if PPV required) Delivery room outcomes and interventions will be summarized and tested between the HI and LO groups and will include 5-minute FiO2, time to reach 80 percent saturation, StO2 over the first 10 minutes, delivery room interventions (PPV, CPAP, intubation, epinephrine, chest compressions, volume, medications) duration of PPV, duration of hypoxia or hyperoxia, average oxygen saturation over 5 minutes, after birth, and Apgar scores.

11d Sample Size Calculation

The study team demonstrated in a large group of infants (n=284) that 35 percent had a low oxygen level (oxygen saturation less than 80 percent) at 5 minutes of life. These infants also had a higher risk of death or brain bleeds (Katheria et al, J Peri 2019). To detect a reduction of 20 percent, each group needs at least 70 infants. This would provide 80 percent power with a two-sided significance level of 0.05.

11e Analysis Sets

The primary analysis for the overall study population will be conducted using an intent-to-treat (ITT) principle: All randomized participants will be included in the ITT population, analyzed according to their assigned treatment groups, regardless of the actual treatment received. An adjudicated dichotomized outcome of peripheral oxygen saturation without any statistical imputation for missing data will be used to conduct the primary analysis for publication.

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11f Baseline Comparability

Maternal and neonatal characteristics and outcomes will be summarized by randomization group. For continuous variables, means/medians and standard deviations/interquartile ranges will be reported. Student's t-tests will be used to compare the differences in continuous variables and when appropriate, medians and quartiles will be reported, and the Wilcoxon rank sum test will be used as an alternative comparison procedure. Categorical measures will be presented as counts and percentages and will be compared using the chi square test of association to identify potential group differences. For rare outcomes such that the chi square test is not appropriate, Fisher's exact test will be used.

Maternal and pregnancy characteristics collected and summarized will include maternal age, gestational age, race and ethnicity, antenatal steroids, magnesium sulfate administration, cesarean section, labor, anesthesia, reason for delivery, placental weight, postpartum delivery-related infection prior to hospital discharge, contamination of sterile field, and umbilical cord venous and arterial pH. Any group characteristics identified as statistically significant between the two groups at a 0.05 level of significance will be considered as covariates in multivariable models in subsequent analyses. Subsequent adjusted analyses will be conducted using logistic regression (dichotomous outcomes), linear regression (continuous outcomes), and longitudinal analyses will use generalized estimating equations (GEE) related to specific study aims. Models will allow for control of potential covariates as well as investigation of effect modification. Standard regression diagnostics will be used to assess model adequacy and to fit the final models.

Additional neonatal characteristics and physiologic data for the first 24 hours after birth will include: NICU admission temperature, lowest and highest hemoglobin and/or hematocrit, peak hematocrit with 24 hours of life, hourly mean arterial blood pressure for the first 24 hours, mean cerebral tissue oxygenation (StO2) over the first 24 hours and the need for medication for low blood pressure. Repeated and longitudinal measures will be examined and potential correlation among multiples using GEE modeling, as appropriate.

Hospital course until 36 weeks corrected gestational age will include variable such as IVH (most severe during hospitalization), bronchopulmonary dysplasia, severe ROP and survival.

11g Adjustment for Covariates

The primary and secondary outcomes analyses will be stratified or adjusted for gestational age strata. Where possible study center and gestational age strata will be used to adjust model-based analyses and test-statistics. Group differences in baseline characteristics will be assessed and if a significant difference between groups is identified they will be used as covariates in exploratory analyses of efficacy end points.

12a Reporting

Table #. Maternal characteristics at baseline (pre-intervention)			
Characteristics	Variable details	Hi Group (N=)	Lo Group (N=)
Maternal			
Race-ethnicity (n, %)	[maternal_race], [maternal_ethnicity]		

Non-Hispanic White	[maternal_race]=5 & [maternal_ethnicity]=2
Non-Hispanic Black	[maternal_race]=3 & [maternal_ethnicity]=2
Non-Hispanic Asian	[maternal_race]=2 & [maternal_ethnicity]=2
Non-Hispanic Native Hawaiian or Pacific Islander	[maternal_race]=4 & [maternal_ethnicity]=2
Non-Hispanic American Indian or Alaska Native	[maternal_race]=1 & [maternal_ethnicity]=2
Non-Hispanic multiracial	[maternal_race]=7 & [maternal_ethnicity]=2
Non-Hispanic unknown race	[maternal_race]=6 or [maternal_race]=UNK & [maternal_ethnicity]=2
Hispanic	[maternal_ethnicity]=1
Other or unknown	[maternal_race]=UNK & [maternal_ethnicity]=UNK
Age (median, IQR)	[maternal age]
At least some college education (n, %)	[education]=5 or 6 or 7
Any diabetes (n, %)	[diabetes]=1
Any hypertension (n, %)	[pih]=1
Intrauterine inflammation or infection (n, %)	[placenta_chorio]=1
Rupture of membranes < 1 hour (n, %)	[rom_1hour]=1
Rupture of membranes >= 1hr before delivery (median, IQR)	[rom_length]
General anesthesia (n, %)	[general_anesthesia]=1
Narcotic during labor (within 2 hrs of delivery)	[narcotic]=1
Multiple delivery (n, %)	[multiples]=1

Table #. Neonatal characteristics at baseline (pre-intervention)

Neonatal	Variable details	Hi Group (N=)	Lo Group (N=)
Race-ethnicity (n, %)			
Non-Hispanic White	[infant_race]=5 & [infant_ethnicity]=2		
Non-Hispanic Black	[infant_race]=3 & [infant_ethnicity]=2		
Asian	[infant_race]=2 & [infant_ethnicity]≠1		
Native Hawaiian or Pacific Islander	[infant_race]=4 & [infant_ethnicity]≠1		
American Indian or Alaska Native	[infant_race]=1 & [infant_ethnicity]≠1		

Hispanic	[infant_ethnicity]=1
More than one race	[infant_race]=7 & [infant_ethnicity]≠1
Other or unknown	[infant__race]=6 or [infant_race]=UNK & [infant_ethnicity]≠1
Mode of delivery	[delivery_mode] [delivery_assisted]
Cesarean	[delivery_mode]=2
Vaginal	[delivery_mode]=1
Gestational age at delivery (median, IQR)	(([ga_weeks]*7) + [ga_days])/7
Sex (n, %)	
Male	[sex]=0
Female	[sex]=1

Table #. Primary & Secondary Outcomes

Outcome	Variable details	Hi Group (N=)	Lo Group (N=)
Achieved SpO2 of 80% by 5 minutes of life (n, %)	Adjudicated primary outcome		
All Grade IVH (n, %)	[ivh_grade]=1 or 2 or 3 or 4		
Grade 3-4 IVH (n, %)	[ivh_grade]=3 or 4		
* Heart rate across the first 10th minute of life	Delivery room continuous data		
Resuscitation interventions (first 10 minutes of life)			
PPV before cord clap (n, %)	[ppv_dcc]		
PPV after cord clamp (n, %)	[support_in_dr_2]=1		
PPV duration (mm:ss)	[ppv_duration]		
Intubation (n, %)	[support_in_dr_3]=1		
Surfactant (n, %)	[support_in_dr_4]=1		
Compressions (n, %)	[support_in_dr_4]=1		
Epinephrine (n, %)	[support_in_dr_5]=1		

*Individual neonate unit of measure=Mean heart rate across each minute

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Table #. Delivery room characteristics (immediately peri-intervention & post-intervention)			
Characteristic	Variable details	Hi Group (N=)	Lo Group (N=)
Breathing before cord clamp (n, %)	[breathing_dcc]=1		
*Start time of CPAP before cord clamp (median, IQR)	[start_time_cpap]		
Apgar score at 1 minute (median, IQR)	[apgar_1]		
Apgar score at 5 minutes (median, IQR)	[apgar_5]		
*Time of cord clamp (median, IQR)	[time_cord_clamp]		

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Table #. Exploratory Outcomes			
Outcome		Hi Group (N=)	Lo Group (N=)
*FiO_2 across the first 10 minutes of life	Delivery room continuous data		
†Duration of Hypoxia (mm:ss) across first 10 minutes of life	Delivery room continuous data		
‡Duration of Hyperoxia (mm:ss) across first 10 minutes of life	Delivery room continuous data		
Mean/Median time to achieve SpO_2 ≥ 80% (mm:ss)	Delivery room continuous data		
*StO_2 across the first 10 minutes of life	Delivery room continuous data		
*StO_2 across the first 24 hours of life	Delivery room continuous data		
*SpO_2 across the first 5 minutes of life	Delivery room continuous data		
*HR across the first 5 minutes of life	Delivery room continuous data		
*MAP (cm H_2O) across the first 10 minutes of life	Delivery room continuous data		
CRIB-II score (IQR)	Delivery room continuous data		
Days on CPAP respiratory support	[crib_score]		
Days on mechanical ventilation	[cpap_days]		
§BP across the first 24 hours of life	[vent_days]		
Surfactant in the first 10 days of life (n, %)	[bp_1_hol] through [bp_24_hol]		
RBC transfusion (n, %)	[surf_nicu]=1		
Number of RBC transfusions	[blood_tx]=1		
PDA with treatment (n, %)	[count_blood_tx]		
Spontaneous intestinal perforation (n, %)	[pda]=1		
‖Necrotizing Enterocolitis (n, %)	[sip]=1		
¶BPD Any Grade (n, %)	[nec]=1		
¶BPD Grade 1 (n, %)	[type_support_bpd]=1 or 2 or 3 or 4		
¶BPD Grade 2 (n, %)	[type_support_bpd]=1		
¶BPD Grade 3 (n, %)	[type_support_bpd]=2		
¶BPD Grade 4 (n, %)	[type_support_bpd]=3		
◊Severe ROP (n, %)	[type_support_bpd]=4		
Use of inhaled nitric oxide (n, %)	[ROP]=1		
Death before discharge (n, %)	[nitric_oxide]=1		
Severe IVH or Death (n, %)	[alive_discharge]=0		
Vasopressors for BP support (n, %)	[alive_discharge]=0 or [ivh_grade]=3 or 4		
Intubated during admission (n, %)	[pressors]=1		
Δ Lowest neonatal Hct	[intubation]=1		
Δ Highest neonatal Hct	[hct_low]		
Δ Lowest neonatal Hgb	[hct_high]		
Δ Highest neonatal Hgb	[hgb_low]		

*Individual neonate unit of measure=Mean FiO_2/SpO_2 across each minute/hour of life
†Hypoxia = SpO_2 < 25th percentile of reference range for SpO_2 after birth for infants <32 weeks GA
‡Hyperoxia = SpO_2 > 97th percentile of reference range for SpO_2 after birth for infants <32 weeks GA
§MAP for each neonate was collected hourly for the first 24 hours of life
‖Modified Bell's stage 2-3
¶BPD criteria as defined in Jensen, Dysart, Gantz et. Al.

◊Stage 3 or 4 treated with laser or Avastin
Definition of abbreviations: MAP= Mean airway pressure; CPAP= Continuous positive airway pressure; BP= Blood pressure; BPD= Bronchopulmonary Dysplasia; CRIB-II= Clinical risk index for babies; PDA=Patent Ductus Arteriosus
Δ within the first 24 hours of life and before transfusion

13a References:

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