ISRCTN12756197 https://doi.org/10.1186/ISRCTN12756197

What is the inspired oxygen fraction that better predicts the need for surfactant administration for the lungs of preterm neonates with neonatal distress syndrome?

Submission date
09/10/2023

Recruitment status
No longer recruiting

Registration date
16/10/2023

Overall study status
Completed

Last Edited
16/10/2023

Condition category
Pregnancy and Childbirth

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Current international guidelines on neonatal respiratory distress syndrome (RDS) recommend continuous positive airway pressure (CPAP) stabilization as the primary treatment. RDS occurs from a deficiency of surfactant, due to either inadequate surfactant production, or surfactant inactivation in the immature lungs. Surfactant replacement is indicated for those babies still requiring a fraction of inspired oxygen (FiO2) > 0.3 (above the normal atmospheric level or 20%) regardless of the gestational age (GA). The research team will explore the accuracy of decreasing FiO2 thresholds as early predictors of surfactant replacement in babies stratified by GA.

Who can participate?
Neonates aged 1 day to 6 months of age with RDS

What does the study involve?
This study is a pragmatic, observational study set in 12 Italian and Spanish neonatal intensive care units (NICUs). This is a secondary analysis of data from a derivation and a validation cohort of preterm babies suffering from RDS, stratified by gestational age (250-276; 280-306; 310-336 days) and stabilized on CPAP. FiO2 was collected soon after stabilization and its prognostic accuracy was evaluated on the subsequent surfactant administration by a rigorously masked physician.

What are the possible benefits and risks of participating?
It is hoped that future patients will benefit from the findings that FiO2 is a GA-dependent predictor of early surfactant administration. Neonates participating in the study have no possible risks because they will not undergo new procedures because of the study itself. It is an observational study without interventions on patients.

Where is the study run from?
University of Naples Federico II (Italy)

When is the study starting and how long is it expected to run for?
May 2017 to April 2023

Who is funding the study?
University of Naples Federico II (Italy)

Who is the main contact?
Prof Francesco Raimondi, raimondi@unina.it (Italy)

Contact information

Type(s)
Public, Scientific, Principal investigator

Contact name
Prof Francesco Raimondi

ORCID ID
https://orcid.org/0000-0003-3250-1582

Contact details
University of Naples Federico II (Università degli Studi di Napoli Federico II)
Via Sergio Pansini 5
Naples
Italy
80131
+ 39 0817463268
raimondi@unina.it

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
Inspired oxygen fraction thresholds accuracy to predict surfactant administration in neonatal RDS is gestational age dependent: a pragmatic, multi-center study

Study objectives
The inspired oxygen fraction (FiO2) has been described as a significant predictor of CPAP failure and subsequent surfactant administration. Current European recommendations are to deliver surfactant if the infant has been stabilized with CPAP 6 cm H2O and still requires a FiO2>0.3

while Canadian guidelines recommend waiting until the oxygen requirement meets an FiO2>0.5. While the American Academy of Pediatrics would only recommend an early (i.e. within 2 hours of life) individualized surfactant administration without citing the FiO2>0.3 cut-off, the latter has been considered by a recent expert consensus from the United States.
Indeed, the choice of any FiO2 threshold is not supported by indisputable evidence. A recent meta-analysis showed no significant difference in major neonatal outcomes (i.e. BPD, ventilation etc) within the FiO2 0.3-0.59 interval. However, it remains unclear whether a FiO2 ≤0.3 threshold may be equally or more beneficial.
We hypothesized that decreasing FiO2 thresholds as predictors of CPAP failure would improve early surfactant replacement.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 15/06/2017, Ethics Committee “Carlo Romano” at the Università Federico II di Napoli (Via Pansini 5, Napoli, 80131, Italy; + 39 331 2642920; segreteria@comitatoeticofedericoiicardarelli.it), ref: 187/17

Study design
Pragmatic observational secondary analysis cohort study

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Inspired oxygen fraction as a predictor of need for surfactant in respiratory distress syndrome of preterm neonates

Interventions
This is a secondary analysis of prospectively collected data from 12 NICUs (Università Federico II, Naples; Ospedale Pineta Grande, Castelvolturno; Ospedale Careggi, Università di Firenze, Florence; Ospedale Buzzi, Milan; Università di Milano, Fondazione Policlinico, Milan; Ospedale Salesi, Università Politecnica delle Marche, Ancona; Fondazione Policlinico Gemelli, Roma; Hospital Gregorio Marañón, Madrid; Hospital San Juan de Dio, Barcelona; Hospital Basurto, Bilbao; and, Hospital Puerta del Mar, Cadiz).

Two cohorts of preterm infants 250-336 weeks of gestational age (GA) were investigated after validating their homogeneity. Neonates were stratified by gestational age calculated from the first day of the last menstrual period: 25-27; 28-30; 31-33 weeks. Written parental consent was obtained and the study was approved by the Ethics Committee “Carlo Romano” at the Università Federico II di Napoli (prot # 1621/17). Formal approval was also obtained by the Ethics Committee of each participating center. The study was conducted in accordance with the TRIPOD statement guidelines.

Preterm neonates were stabilized after birth as per the individual NICU protocol. After CPAP stabilization and within 120 minutes of life, a local investigator who was not in charge of the patient recorded the quantity of respiratory support in cm H2O, her/his FiO2 and the post-natal

age. SpO2 was recorded at the right hand by pulse oximetry, and it was maintained in the 90-95% range by adjusting FiO2. Natural surfactant (poractant alfa 200 mg/kg for the first dose and 100 mg/kg for the following doses, Chiesi Farmaceutici, Parma, Italy) was prescribed by an attending neonatologist, unaware of the purpose of the study, based on radiographic and clinical signs suggestive of respiratory distress syndrome (RDS) as per the individual NICU protocol. For each patient, the local investigator also recorded the subsequent respiratory support history, the clinical complications from birth to discharge/exitus, and the presence of BPD.

Intervention Type
Other

Primary outcome(s)
FiO2 thresholds recorded within the first 3 hours of life as predictors of later surfactant administration in preterm neonates by a masked attending physician measured using a secondary analysis of prospectively collected data at one timepoint

Key secondary outcome(s))
The following secondary outcome measures were measured using prospectively collected data at one timepoint:
1. Gestational age, birth weight, type of delivery, chorioamnionitis, maternal hypertension, PROM, IUGR, Apgar score at 5 min ≤5, and antenatal steroids recorded within 120 minutes of life
2. First surfactant dose administered (number of infants)
3. Age at first surfactant dose (minutes)
4. FiO2 at first surfactant dose
5. Death or BPD at NICU discharge

Completion date
30/04/2023

Eligibility

Key inclusion criteria
Premature neonates with respiratory distress syndrome (RDS) enrolled at birth and before the administration of the first surfactant dose. RDS in the preterm infant was defined as the presence of intercostal and subcostal retractions with expiratory grunting shortly after birth in the presence of typical radiographic features.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Neonate

Lower age limit
1 days

Upper age limit
6 months

Sex
All

Total final enrolment
412

Key exclusion criteria
1. Infants who were intubated in the delivery room
2. Neonates with major congenital malformations

Date of first enrolment
01/05/2018

Date of final enrolment
31/10/2022

Locations

Countries of recruitment
Australia

Italy

Spain

Study participating centre
Federico II University Hospital
Division of Neonatology, Department of Translational Medical Sciences
Via Pansini 5
Naples
Italy
80131

Study participating centre
NICU Casa di Cura Pineta Grande
Via Domitiana
Castel Volturno (CE)
Italy
81030

Study participating centre

Neonatology Division, Instituto de Investigación Sanitaria Hospital General Universitario Gregorio Marañón, Complutense University of Madrid
C/ O´Donnell, 48-50
Madrid
Spain
28009

Study participating centre
Neonatal Intensive Care Unit, Department of Paediatrics, Hospital Germans Triasi Pujol, Autonomous University of Barcelona
Passeig Sant Joan de Déu, 2
Barcelona
Spain
08950

Study participating centre
NICU, Vittore Buzzi Children's Hospital
Via Castelvetro 32
Milan
Italy
20154

Study participating centre
Department of Clinical Sciences and Community Health, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Cà Granda Ospedale Maggiore Policlinico, University of Milan
Via della Commenda 12
Milan
Italy
20122

Study participating centre
Women's and Children's Health Department, University of Padova
Via Giustiniani 2
Padova
Italy
35128

Study participating centre
Division of Neonatology, Careggi University Hospital of Florence
largo Brambilla 3
Florence

Italy
50134

Study participating centre
Neonatal Intensive Care Unit, Puerta del Mar University
Avenida Ana de Viya 21
Cadiz
Spain
11009

Study participating centre
Neonatal Intensive Care Unit, Basurto University Hospital
Montevideo Etorb., 18,
Bilbao
Spain
48013

Study participating centre
Newborn Research Centre, The Royal Women's Hospital, University of Melbourne
Grattan Street
Parkville. Victoria
Australia
3010

Study participating centre
TIN Ospedale Salesi, Università Politecnica delle Marche
Via Conca, 71 - Torrette
Ancona
Italy
60126

Study participating centre
TIN Fondazione Gemelli. Università Cattolica del Sacro Cuore
Largo Agostino Gemelli 8
Roma
Italy
00168

Sponsor information

Organisation
University of Naples Federico II

ROR
https://ror.org/05290cv24

Funder(s)

Funder type
University/education

Funder Name
Università degli Studi di Napoli Federico II

Alternative Name(s)
University of Naples Federico II, University of Naples, Federico II University of Naples, Università di Napoli, Università di Napoli Federico II, UNINA

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
Italy

Results and Publications

Individual participant data (IPD) sharing plan
The dataset generated and /or analyzed during the current study will be available upon request from Prof Francesco Raimondi, raimondi@unina.it. Anonymized data will be available for sharing for one year after the publication of the study.

IPD sharing plan summary
Available on request