Feeding Interventions Because of Respiratory Events in Preterm Infants – FIBRE: Protocol v1.4

Are feeding-related interventions effective in reducing respiratory events in preterm infants?

Plain Language Introduction to FIBRE

Breathing events are common in premature babies cared for in the Newborn Care Unit. These include apnoea (pauses in breathing), desaturations (drop in blood oxygen) and bradycardia (reduced heart rate). Such events are important as they have the potential to impact on long-term brain development. Breathing events occur more frequently during and after feeding.

A number of measures are in common practice in many neonatal units, include posture (changing the baby's position during feeding) and feed rate (how quickly the feed is given through the feeding tube). To date, there is not all that much research exploring the benefit of such interventions in reducing breathing events. Finding an answer to this question will help us in deciding how to best manage and minimise breathing events in this and other neonatal units.

We aim to test the hypothesis that feeding interventions, such as alternative positioning and slowing the feeding rate may reduce frequency of breathing events in premature babies. This will be done by exposing each baby to three feeding conditions over a three-day period and comparing the number of breathing events which occur under each condition.

Our study population is babies who were born premature (i.e. born less than 32 weeks gestation) who are now breathing by themselves (i.e. not requiring respiratory support) and who are receiving full milk feeds through a feeding tube (i.e. are not receiving nutrition through a vein/cannula and are not yet breast or bottle feeding).

Each baby will experience each of the test conditions over a 24 hour period, and will therefore take part in the study for a total period of 3 days. During this time, we will be measuring the number of respiratory (breathing) events, and the time spent in different oximetry (blood oxygen level) ranges. These are measured by cot-side monitors – these monitors are used routinely for every baby managed in the Newborn Care Unit, so babies will not need to undergo any additional testing. The order that each baby proceeds through each test condition will be random. The test conditions that each baby will experience are as follows:

1. Care as usual (baby nursed flat on back, with normal tube feeds)
2. Positional intervention (baby nursed on stomach with the cot propped, with normal tube feeds)
3. Feed rate intervention (baby nursed flat on back, with tube feed given over 45min).

Background

Respiratory events, including apnoea, occur frequently in preterm infants and are often the subject of interventional apprehension in the neonatal unit. This is particularly true in the context of feeding, where gastric distension and impeded functional residual capacity may precipitate respiratory events at greater frequency[1]. Prolonged apnoeic events are often followed by bradycardia and hypoxia, which may impair tissue oxygenation and perfusion during critical periods of growth and development. Minimisation of respiratory events is desirable and has been pursued with good evidence through the use of methylxanthines[2-4] and respiratory support[5]. Feeding-related interventions, including changes in infant positioning and feed rate changes, are frequently initiated in response to respiratory events without a clear basis in evidence. These include manipulation of infant positioning (prone vs. supine), elevation (propped vs. flat) and feeding rates (nasogastric bolus vs. continuous pump). Few studies to date have explored the relative benefits of these interventions. This study aims to determine the effects of feeding interventions on the frequency of respiratory events in preterm infants managed in a neonatal unit.

Respiratory Events and Feeding

Establishment of a normal respiratory pattern is a major developmental milestone for preterm infants[6]. Apnoea, in the context of prematurity, is a pause in breathing of more than 15-20 seconds, and/or accompanied by oxygen desaturation (SpO2 ≤ 80% for ≥ 4s) and bradycardia (heart rate <2/3 of baseline for ≥4 seconds), in infants born less than 37 weeks of gestation[7, 8]. It is common in the preterm population, occurring in nearly all infants born at <29 weeks, 54% at 30 to 31 weeks, and 15% at 32-33 weeks gestation[9, 10].

While there is certainly baseline variability in respiratory function, a number of factors are thought to modify the frequency and severity of events[11]. Apnoea is inversely associated with gestation at birth (GA) and birthweight (BW)[6]. Classification of apnoea is generally Central, Obstructive or Mixed. Central apnoea may reflect a relative immaturity of the respiratory centres of the brain, or may occur as a result of central nervous system disease (intracranial haemorrhage, hypoxic ischaemic encephalopathy)[6] or systemic disease (infection, glucose or electrolyte imbalance[12] or thermoregulatory dysfunction[13]). Obstructive apnoea occurs as a result of pharyngeal or airway collapse or apposition[12]. In many babies apnoea may result from mixed central and obstructive factors. Apnoea does occur more frequently in the context of feeds, and potential mechanisms for this have included gastric distension, reduced functional residual capacity and upper airway changes[14]. Gastro-oesophageal reflux has also been associated with apnoea in this population[15], however the pathological significance of this has been debated[16-18].

Short term consequences of apnoea include desaturation, bradycardia and requirement for increased respiratory support, along with the sequelae of supplemental oxygen exposure[7]. Long-term consequences are controversial, due to the possibility of coincidental neurological injury in the context of prematurity[19, 20]. Some studies have, however, implicated apnoea in neurodevelopmental disturbance beyond the neonatal period[21].

State of the Literature

A systematic review of the literature did not identify any previous studies which have looked at the effects of position or feed rate on respiratory events during and after feeds in this population. A number of studies have compared bolus to continuous nasogastric feeds, but none have specifically examined the rate at which the bolus feed is administered and with these outcome measures. Similarly, multiple studies have described the effect of position on cardiopulmonary mechanics either outside the context of feeds, or without describing the frequency of respiratory events. Others have examined the effect of position during feeds, but in older infants and in the context of suck feeding. No studies were identified which specifically tested our hypothesis.

Feed Rate (pump vs. gravity)

The National Center for Biotechnology Information (NCBI) Pubmed database was queried using the following search string:

> *((((gavage OR gravity OR pump OR continuous OR rate)) AND (feeds OR feed OR feeding)) AND (preterm OR premature OR prematurity)) AND ("respiratory event" OR "respiratory events" OR apnoea OR apnea OR apnoeic OR apneic OR bradycardia OR bradycardic OR hypoxia OR hypoxic)*

A 2012 Cochrane systematic review examining pump vs. gravity only identified a single small crossover trial which precluded extensive meta-analysis[22]. This 1994 trial involved 31 babies and measured outcomes of respiratory rate and heart rate before, during and after feeds[23]. The study identified a trend towards increased respiratory rate following push gavage feeds however this did not reach statistical significance.

A small number of trials have examined nasogastric bolus vs. continuous feeds. A Cochrane meta-analysis of 7 trials and 511 infants evaluating continuous vs. bolus nasogastric feeds found no difference in respiratory events[24]. One study did, however, suggest a trend towards increased apnoeas with continuous feeds[25]. A subsequent 2014 crossover trial involving 33 preterm infants also associated continuous feeding with an increased number of apnoeic events and consequent hypoxia which was statistically significant[14].

Infant Position

The NCBI Pubmed database was queried using the following search string:

> *(((positioning OR position OR positional OR elevation OR supine OR prone)) AND (feeds OR feed OR feeding)) AND (preterm OR premature OR prematurity)*

Many studies have explored the mechanical and cardiopulmonary effects of position on the preterm infant, both in terms of gastric residuals[26-28] and in heart rate variability and respiratory dynamics[11, 29, 30]. Prone positioning may improve thoracoabdominal synchrony[11] and has been associated with superior oxygenation and improved functional residual capacity in babies who were supplemental oxygen-dependent, but not in those who were not requiring additional oxygen support[31]. Others have looked at the effects of position on respiratory events in older infants, usually in the context of oral/suck feeding[32, 33]. Additional studies have shown that alternative positioning has positive effects on sleep[34] and development[35], and potentially in reducing gastro-oesophageal reflux and feed intolerance[36-38]. No studies have looked at interventions during/after feeds for respiratory events in this population.

Aims / Hypothesis

This study aims to determine the effects of feeding interventions (infant and cot positioning, pump *vs* gravity feeds) on the frequency of respiratory events in preterm infants managed in a neonatal unit.

- We hypothesise that feeding interventions such as alternative positioning and pump tube feeds may reduce frequency of respiratory events in preterm infants.
- This may inform clinical practice by neonatal medical and nursing staff who are caring for this vulnerable population.

Study Population

Plain Language

The infants in this study consist of well babies who were born prematurely, less than 32 weeks' gestation, who are breathing by themselves (not needing respiratory support) and who are being fed by a feeding tube.

Inclusion Criteria

Preterm Infants < 32 weeks gestation at birth can be enrolled in the study and become eligible once they meet the additional criteria below:

- Off respiratory support for at least 5 days
    - Infants who are on low flow sub-nasal oxygen < 0.5 L/min are eligible (oxygen flow rate will not be weaned during the trial)
    - Infants who are receiving Caffeine Citrate will not be excluded, but the caffeine dose will only be adjusted for body weight during the trial and will not be discontinued during the trial regardless of gestational age
- Receiving full enteral feeds (>=150 mL/kg/day) for at least 5 days
- Receiving 3 hourly feeding for at least 48 hours

Exclusion Criteria

- Currently receiving respiratory support:
    - High-flow nasal cannula therapy (HFNC)
    - Continuous Positive Airway Pressure (CPAP)
    - Nasal Intermittent Positive Pressure Ventilation (NIPPV)
    - Conventional or Oscillatory Ventilation
- Significant comorbidity:
    - History of confirmed necrotising enterocolitis (NEC)
    - Past surgery or condition likely to require surgery (other than inguinal hernia)
    - Significant or symptomatic congenital heart disease
    - Congenital airway obstruction (Pierre-Robin Sequence etc.)
- Discharge likely to occur during the trial
- Receiving nutritive suck feeds (breast or bottle feeds)
- Receiving treatment for Gastro-oesophageal Reflux Disease (GORD)
- Infants for whom a decision to provide palliative care has been made

Outcomes

Plain Language

We will be measuring the number of respiratory (breathing) events, and the time spent in different oximetry (blood oxygen level) ranges.

Definitions

For the purposes of this study, the following definitions will be used:

- Respiratory event
  - clinically significant apnoea *and/or*
  - clinically significant desaturation *and/or*
  - clinically significant bradycardia
- Apnoea
  - clinically significant apnoea was defined as a pause in breathing, as measured by the Philips cotside monitor, which:
    - lasts more than 15s in duration, *or*
    - was accompanied by clinically significant desaturation and/or bradycardia as defined below, *or*
    - required intervention (manual stimulation, PEEP or IPPV)
- Bradycardia
  - clinically significant bradycardia was defined as heart rate < 100 for ≥ 5s as measured by Philips cotside monitor with a 5s averaging time
- Desaturation
  - clinically significant oxygen desaturation was defined as SpO2 < 80% for ≥ 5s as measured by Philips cotside monitor with a 5s averaging time

Primary Outcomes

This study will measure the number of respiratory events and oximetry histograms during each of the 24h condition periods:

- Number of respiratory events:
  - Defined as total number of clinically significant:
    - Apnoeic events
    - Desaturations
    - Bradycardic events
- Percentage of time spent with SpO2 < 80% over the 24h testing period

Secondary Outcomes

- Percentage of time spent with SpO2 >= 88% over the 24h testing period

Effect Size

A clinically significant effect was defined for each of the three outcomes:

- 40% reduction in number of respiratory events
- 50% improvement in percentage of time spent with SpO2 >= 88% over the 24h testing period
- 50% reduction in percentage of time spent with SpO2 < 80% over the 24h testing period

Data Collection

The following demographic and clinical data will be recorded for each infant on enrolment in order to describe our sample:

- Gender
- Gestational age at birth
- Chronological age and Corrected gestational age
- Birth weight
- Current weight
- Feed volumes (mL/kg/day)
- Caffeine administration

All infants enrolled in the study will be monitored using the same standard cardiorespiratory monitoring and nursing observations employed for all babies managed in the unit. The following clinical data will be recorded in order to test the primary hypothesis:

- Number of respiratory events
    - Apnoeas, desaturation and bradycardic events, as defined previously, will be counted and totalled for each 24 hour period by retrospective review of the central monitor. This data will also be reconciled with a nursing observation sheet in order to identify issues with lead contact, cares or events requiring intervention.
- Oximetry histogram
    - The percentage of time spent with oxygen saturations >= 88% and <80% will be recorded using the histogram feature of the Philips monitors at the cot-side at the conclusion of each 24 hour condition period

Blinding

Data collection for number of respiratory events will be blinded, as it relies on examining the monitoring trace for each 24 hour condition period and counting the number of events. While the trace will identify which baby is being monitored, the researcher counting the events will be blind to the test condition for each 24 hour period. The histogram data is completely objective, derived from the monitors, and can be printed at the end of each 24h condition period.

Study Design

Design

This study will employ a randomised triple crossover design. In this approach, each infant will experience each of the three test conditions in a sequence which is randomised. Thus each infant will serve as its own control, and variance within and between infants can be measured. Benefits of a crossover design include smaller sample size requirements compared to equivalent parallel-group trials in order to meet the same criteria in terms of type I and type II error risks[39]. In addition, each infant is managed equivalently in every respect, excepting the actual order of the test conditions experienced – thus no infant should be advantaged or otherwise relative to the other infants enrolled in the study as each infant is exposed to the same conditions.

In general terms, crossover design is appropriate when:

- The underlying disease is similar during all treatments, i.e. not cured by one of the treatments and not of a short duration relative to the treatment period. It is necessary to separate period effects from treatment effects. This is the case in this study, as we are examining respiratory events which occur as a result of feeding. A feed-related intervention should only have any effect on events during and after the actual feed, and will not be curative of respiratory events in subsequent feeds.
- The variation in the outcomes for each baby is smaller than the variation between babies, else any benefits conferred by employing a crossover design are negated. Pilot serial measurements of both primary outcomes on n = 10 babies meeting eligibility criteria confirmed this to be the case in this population.
- The treatment effect is ideally restricted to the period in which it's applied. In this study, any potential benefit of a feed-related intervention should be limited to the short time during and immediately after a feed and should then be abolished. In addition, one of the test conditions is a 'care as usual' approach, further diminishing the role of any washout period (in which the care employed would simply be 'care as usual').

Test Conditions

The interventions proposed in this study are used fairly commonly in neonatal units in Australia and internationally – this study aims to establish whether there is an evidence base for doing so. While a 'supine/flat/gravity-fed' nursing paradigm might be considered by most to be standard or default practice, there is a lack of consensus, hence the impetus for this study.

Infant Position

Most infants in this population are nursed in an isolette or cot, and may be positioned supine (laying on back) or prone (laying on front). Infants are often nursed in different positions based on clinical indications (for example, avoiding pressure areas or in response to respiratory distress). In addition, the cot may be positioned in such a way that the baby lies neutral (flat) in the horizontal plane or is elevated (propped). Routine practice for feeds would generally involve the baby being fed while lying flat on his/her back with the cot in a neutral position.

Feed Rate

Nutritional requirements vary with the post-gestational age and condition of any given baby. Most preterm infants will progress temporally from parenteral nutrition (provided through a cannula) to enteral nutrition with a nasogastric tube (feeding tube) to suck feeds (breast or bottle feeding) before being considered suitable for discharge. Nasogastric feeds may be administered continuously by pump (given at a continuous rate measured in mL/hr) or more commonly, bolus (a volume of milk/formula is given at a particular time interval, usually every 2 to 3 hours). Furthermore, bolus feeds may be given by gravity ('as quickly as the tube will accommodate') or pump (a rate can be specified to give the feed over a longer period of time). Most babies begin enteral feeds as bolus feeds with smaller volumes given every 2 hours, and then progress to 3 hourly feeds. Such feeds are usually administered by gravity bolus, however clinical factors may warrant reducing the feed rate (e.g. giving the same bolus volume over 45min).

Infants will undergo test conditions in combinations of feed and position conditions, as outlined in Table 1. Infant and cot positional interventions, where possible, will be maintained throughout the entirety of the 24h condition period, with the exception of routine nursing cares and brief interactions with parents and caregivers.

Table 1: Test Conditions Employed in the FIBRE Study

	Infant Position	Cot Position	Rate of Feed
Condition A Control	Supine	Flat	Bolus gravity feed
Condition B Position intervention	Prone	Propped (15 degrees)	Bolus gravity feed
Condition C Feed rate intervention	Supine	Flat	Continuous pump feed over 45 min

Timecourse

Each condition continues for 24 hours before switching to the next condition. Thus each infant will experience each intervention over a 3 day period of enrolment, with the order of progression through conditions randomly assigned. No washout period will be required between conditions, as respiratory events should be related to the period during and immediately post-feed (i.e. the effect of the previous test condition should have disappeared well before the first feed in the next test condition).

Randomisation

Infants will be randomly assigned to one of six sequence groups ABC/ACB/BCA/BAC/CAB/CBA, as outlined in Table 2. This will permit assessment of potential period effects and carryover effects, as each treatment follows every other treatment at least once in the six sequence design, as opposed to a simpler Latin Square approach. Randomisation will be achieved through the use of a computer generated sequential list, thus dictating the sequence of conditions.

Table 2: Test Conditions Employed in the FIBRE Study

Group	Sequence Group
1	ABC
2	ACB
3	BAC
4	BCA
5	CAB
6	CBA

Size and Power Considerations

We will use a 5% significance level (α = 0.05) for all comparisons. The expected sample was sized using a two-sided test, as there is no strong expectation that effect size would only be in one direction. A small pilot was conducted using n = 10 babies using existing monitor data, and measuring three outcomes sequentially over three days for each baby:

- Number of respiratory events (primary outcome)
- Percentage of time spent with SpO2 < 80% over the 24h testing period (primary outcome)
- Percentage of time spent with SpO2 >= 88% over the 24h testing period (secondary outcome)

The observed baseline data was right-skewed, thus a log transformation was applied. The between ($\sigma_s{}^2$) and within subject variance (σ^2) were estimated by fitting a variance components model to the log-transformed baseline audit data for each of the three outcomes.

The sample size formula for a two-sided cross-over study design is shown in Equation 1, where n_c is the minimum total sample size required for cross-over design, and $Z_{\frac{\alpha}{2}}$ and Z_β are the values of the standard normal distribution that cut off probability $\frac{\alpha}{2}$ and β in the upper tail respectively, σ^2 is the within-subject variance and Δ is the minimum difference to be detected. For cross-over studies the variance term depends only on the within-subject variance:

$$n_c = \frac{2\left(Z_{\frac{\alpha}{2}}+Z_\beta\right)^2(\sigma^2)}{\Delta^2}$$

The correlation between two observations from the same subject (ρ) is given by $\rho = \sigma_s{}^2/(\sigma_s{}^2 + \sigma^2)$. The more correlated the observations from the same subject (i.e. the closer ρ is to 1), the smaller the sample size required for a cross-over design compared to an equivalent parallel design. Baseline audit data showed a correlation of approximately 0.6 for the number of events and correlations approximating 0.4 for the histogram outcomes; hence the required crossover sample size is much smaller for all three outcomes of interest to achieve similar power.

A clinically significant effect was defined for each of the three outcomes based on considerations of an effect which might modify practice:

- a 40% reduction in number of respiratory events (n_c= 87 infants, 1 – β = 0.8)
- a 50% improvement in percentage of time spent with SpO2 >= 88% (n_c = 79 infants, 1 – β = 0.8)
- a 50% reduction in percentage of time spent with SpO2 < 80% (n_c= 108 infants, 1 – β = 0.8)

A sample size of 90 infants would produce a study with 80% power to compare both primary outcomes, and 70% power to compare the secondary outcome.

Design Consultation

Consultation has been sought from a senior statistician at Griffith University (Gold Coast, Australia) and through a private Consultant Statistician (Data Analysis Australia Pty Ltd) which has guided design. One of the associate researchers is a consultant neonatologist with experience in education and research, and has been actively involved in the proposal design and offered clinical perspective on design parameters and outcomes. We have also sought and utilised advice from the Clinical Director of the Newborn Care Unit in which the study is taking place, as well as other neonatologists in the unit, particularly in relation to defining clinically significant effect sizes.

Analysis

A mixed effect model will be employed to analyse this crossover study. This approach has the advantages that all three treatment effects for a given outcome can be modelled together, and incomplete records in the case of dropouts can still contribute to the model fit and the method can handle unbalanced data. Standard analysis methods exclude incomplete records and so the study can quickly become underpowered when patients don't complete all treatments.

Consent

Parents or caregivers of infants who will prospectively be expected to meet eligibility criteria will be approached in the first week or two after birth by a member of the research team, or by medical or nursing staff who have attended a training in-service regarding the study. A verbal introduction will be provided outlining the purpose, process, timeframes and outcomes and other specifics of the study, and opportunity will be provided to answer any queries. A written information pack will also be provided at this time, which will include the scope of consent. It will be emphasised that election not to participate in the study will in no way affect the care provided in the Newborn Care Unit.

Expenses

There are no formal funding arrangements for this study and funding requirements are minimal. Technology infrastructure is in place and used as part of routine management in the unit already. Primary resource required is research team's time, some of which will occur during work hours and much of which will be freely volunteered. Statistical support will be sought, where possible through the Gold Coast Health service, or Griffith University, and any funding shortfall will be self-funded.

Ethics

A National Ethics Application Form (NEAF) application has been submitted through Australia Online Forms for Research (*https://au.ethicsform.org/)*

Local approval has been sought and obtained through the Gold Coast Hospital and Health Service Human Research Ethics Committee (HERC) (EC00160) and a Site-Specific Approval has been obtained.

Site Location

Newborn Care Unit: Block D, Level 3
Gold Coast University Hospital
1 Hospital Blvd
Southport QLD 4215

Timeframe

Anticipated Start Date: 15/06/2016
Anticipated Completion Date 31/12/2018

Research Team

Primary Researcher

Dr. Chris Richmond *MBBS BBiomedSc* (Paediatric Registrar, Gold Coast University Hospital)

Research Supervisor, Associate Researcher

Dr. Pita Birch *FRACP, MBBS* (Consultant Neonatologist, Director of Paediatric Physician Education, Gold Coast University Hospital)

Assistant Researcher

Dr. Courtney Jennings *BMed* (Paediatric Senior House Officer, Gold Coast University Hospital)
Fabian Ring MBA, BBiomedSc (Hons) (Medical Student, Bond University Hospital)

Research Nurses

Lacey Richmond *RN* (Registered Nurse, Gold Coast University Hospital)
Sheree Taylor RN RM (Registered Nurse, GCUH)
Erika Rossouw *RN RM GradDip Neonatal Nursing* (Clinical Facilitator, GCUH)
Lisa Wright *RN RM GradCert Neonatal Nursing LLB (Hons)* (Clinical Facilitator, GCUH)

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