May 31, 2018 Version 1

Prevention of hypoglycaemia in a resource-poor setting with oral 10% dextrose in low birth weight newborns: A randomized controlled trial V.1

DOI
dx.doi.org/10.17504/protocols.io.qijducn

Dominik Metz[1], Sara Chiurchiù, Emanuele Bottosso, Giuseppe Pontrelli, Martina Mazzocco, Lucilla Ravà

[1]CUAMM, Doctors with Africa

Dominik Metz

OPEN ACCESS

DOI: dx.doi.org/10.17504/protocols.io.qijducn

Protocol Citation: Dominik Metz, Sara Chiurchiù, Emanuele Bottosso, Giuseppe Pontrelli, Martina Mazzocco, Lucilla Ravà 2018. Prevention of hypoglycaemia in a resource-poor setting with oral 10% dextrose in low birth weight newborns: A randomized controlled trial . **protocols.io** https://dx.doi.org/10.17504/protocols.io.qijducn

Protocol status: Working
We use this protocol and it's working

Created: May 29, 2018

Last Modified: May 31, 2018

Protocol Integer ID: 12587

Keywords: neonatal hypoglycaemia, 10% dextrose, low birth weight

Abstract

Project Summary

Background Rationale

Neonatal hypoglycaemia is a common condition, particularly affecting LBW newborns, and is associated with both acute and long standing complications. Ideally, the mother can provide breast milk as soon as possible; however, in many circumstances (poor nutrition of mother, post-operative Caesarian section, etc) this may not be the case for hours or even days. If resources are available, this can be managed by providing the LBW neonate with artificial milk/donor whilst waiting for breast milk when required. However, this is often not available in resource poor countries due to expense and difficulty in production (timely clean safe water, training in how to make the milk etc). Furthermore, in resourced hospitals, glucose is monitored in at risk babies, and should they develop hypoglycemia, IV 10% dextrose can be relatively simply administered. In resource poor settings, this is challenging- firstly, glucose monitoring and then the administration of IV 10% dextrose require resources, skills and nursing that are often not available. The primary aim of this study is to assess whether the use of oral 10% dextrose, is tolerable and reduces the incidence of hypoglycaemia in LBW newborns in the absence of sufficient maternal breast milk. 10% dextrose is readily available, inexpensive and can be stored at room temperature.

Objectives

Our aim was to assess whether hypoglycaemia could be prevented in LBW babies with insufficient maternal breast milk (MBM), by supplementing their feed with oral 10% dextrose.

Methods

This is a 8 months, interventional, prospective, single centre, randomised, double arm control trial on 74 newborns conducted at a district hospital in Tanzania (Tosamaganga Hospital) where Doctors with Africa - CUAMM has ongoing projects on maternal-neonatal health. LBW newborns fulfilling the inclusion criteria will be randomly allocated to either the intervention (supplemental oral 10% dextrose) or monitoring arm. Glucose will be monitored regularly in both arms and the incidence of hypoglycaemic episodes recorded together with normal vital signs. A budget of 16,000,000Tsh has been proposed for the study.

Outcomes

The primary outcome will be hypoglycemia (<2·6mmol/L) in the first three days of life.

1 **Inclusion Criteria**

Neonates in the first day of life satisfying the following inclusion criteria will be eligible to participate in the study:
1. Birth weight <2500 g
AND
2. Parental consent; a written informed consent will be obtained by a member of the neonatal team involved in the study from a parent or guardian before treatment.

2 **Exclusion Criteria**

Neonates with any of the below criteria will be excluded from the study
1. Parental refusal to participate to the study
OR
2. Major congenital malformations
OR
3. Birth weight less than 1500 g (VLBW)
OR
4. Signs of significant respiratory distress syndrome (Respiratory Rate >80, grunting)
OR
5. Birth Asphyxia (classified by APGAR score less than 7 at 10 minutes)

3 **Consent**

Obtained (Appendix 2) by a trained research nurse; written in local Language (Kiswahili) and English. If unable to unable to read, assisted by research nurse and thumb print used as signitature. An information sheet was also provided for the mothers.

consent form english.pdf

consent form kiswahili.pdf

patient information sheet english.pdf

patient inforamtion sheet kiswahili....

4 **Randomisation and masking**

By simple computer-generated randomization list, to assign babies (1:1) who fit the criteria to either Dextrose or Control arm. Randomisation list will be determined off-site by a methodologist who will email the sequence and this will be stored in a closed envelope.
Clinicians, families and all study investigators will be masked until enrollment: the arm allocation of the single patient will be disclosed just after the enrollment, and then the name of the patient associated to the number and treatment assignment reported in the list.

5 **Demographics**

Background demographics of the mother, baby and delivery will be recorded on the data monitoring sheets (see appendix);

data collection form english.pdf

data sheet kiswahili.pdf

6 **Arm D:**
The optimal 2 hourly feed volume will be given; 10% dextrose will be used to attain this volume if the EBM amount is insufficient. Daily fluid requirement will be used as by the WHO (1) (see appendix 1). Specially trained neonatal study nurses will monitor the feed and measure the amount of 10% dextrose/EBM using 10ml and 20ml measuring cups/syringes as appropriate.
-Day 1: 60 ml/kg ÷ 12 to give optimal 2 hourly feed quantity
-Day 2: 80 ml/kg ÷ 12 to give optimal 2 hourly feed quantity
-Day 3: 100 ml/kg ÷ 12 to give optimal 2 hourly feed quantity
Feeding will be 2 hourly by cup. The amount of milk and the amount of additional 10% dextrose provided will be documented on Data collection sheet (Appendix 1).
Once more than 70% of the daily fluid requirement is produced, oral 10% dextrose will no longer be provided, milk quantity will continue to be recorded.
The neonatal study nurses will each be provided with a timer in order to be able to monitor when feeds are due.

7 **Arm C:**
The baby will receive only EBM. The amount of EBM produced will be recorded 2 hourly. Specially trained neonatal study nurses will monitor the feed and measure the amount of EBM using 10ml and 20ml measuring cups/syringes as appropriate.
In both arms, additional breast feeding (BF) will be encouraged post EBM as will skin-to-skin contact.

8 **Monitoring**
In both arms, pre-feed Glucose will be measured using Accu-Chek Active meter at 1, 3, 5, and 7 hours after birth; then 4 hourly for 2 days; and then 6 hourly on the third day. All recordings will be made on a separate data collection sheet (see appendix 1)

Vital signs (respiratory rate, heart rate and temperature) will be monitored 2 times per day, and more frequently if abnormal or concern; Body weight will be measured at birth and daily thereafter; All parameters will be documented on a separate pro-forma (for nurse and doctor involved in study). A nurse will be present at all times and a pediatrician will be available at all times if needed.

vital signs for study.pdf

newbron vital signs chart.pdf

9 **Rescue Plan**
1. If at any point in both arms the glucose is less than 2.6 mmol/L, feeding will be given immediately (the required amount +/- Dextrose 10%) and the glucose will be rechecked 1 hour post feed.

2. If at any point in both arms the glucose is less than 1.1 mmol/L the participant will receive 2 ml/kg IV 10% dextrose and the glucose will be rechecked in 1 hour.
3. If patient develops clinical signs of Necrotising Enterocolitis (vomiting, blood in stool, absent bowel sounds and abdominal distention), fluids will be switched to IV and antibiotics commenced.
4. If patient develops signs of sepsis, IV antibiotics will be commenced (Ampicillin 50 mg/kg BD & Gentamicin 5 mg/kg OD) as per internationally (WHO) recognised protocols.
5. If patient develops clinical signs of dehydration and the mother does not have sufficient breast milk, oral or IV 10% dextrose will be provided depending on clinical judgement.

10 **Adverse Events**

Specifically, monitoring will aim to detect any deviances in the following;
serious adverse events and adverse events comprehensive of : death, dehydration (defined clinically including parameters of dry membranes, skin turgor, increased capillary refill time), necrotizing enterocolitis (modified Bell's criteria), sepsis (defined clinically- respiratory distress, lethargy or hypotonia, feeding intolerance, temperature instability, evidence of poor perfusion and increased heart rate), diarrhoea (increased frequency of evacuation and presence of watery or green stool, or contained mucus or blood), hyperglycaemia (> 10 mmol/l), respiratory distress syndrome (grunting, respiratory rate>80, saturations <90%).

11 **Withdrawal**

If any patient develops any significant or unforeseen side effects or if the mother retracts consent they will be removed from the trial and continue with routine neonatal care. This will be documented and shared with the safety monitoring group.

12 **Primary outcome Measures:**

The primary outcome is the frequency of hypoglycaemia, classified as moderate (<2,6 and > 1,1 mmol/l) and severe (< 1,1 mmol/l) during the first 3 days of life.
In all participants, glucose will be controlled using the glucometer pre-feed at 1, 3, 5, and 7 hours after birth; then 4 hourly for 2 days; and then 6 hourly for day 3.

Note

In the original protocol we did not clarify the exlusion of baseline (first hour, prior to intervention) hypoglycaemic episodes. Whilst we implied this in the hypothesis, we now make clear that the primary outcome was not including baseline (1st hour) hypoglycaemic episodes. We also clarrify that we assessed the primary outcome as number of babies who developed a hypoglycaemic episode. We went on to also analyse number of (repeated) episodes and number of episodes per baby.

13 **Secondary Outcome Measures:**

Secondary outcomes were

(i) Time to establish adequate MBM production (defined for the purpose of this study as >70% of calculated fluid requirement as recommended by the WHO);
(ii) Body weight at the fourth day of life;
(iii) Treatment of hypoglyceamia with oral 10% dextrose
(iv) Significant side effects.

14 **Study Site**

The study will be conducted at a district hospital in Tanzania (Tosamaganga Hospital) where Doctors with Africa CUAMM has ongoing projects on maternal-neonatal health.

15 **Data Analysis**

Analysis will be conducted comparing the number of hypoglycaemic episodes observed in both arms of the trial. Data will be collated onto a PC available at Tosamaganga Hospital and transferred to Excel spreadsheet. The data will be used to produce incidence of hypoglycaemia in each group and using statistical software for analysis we will be able to see if our null hypothesis can be rejected (see sample size calculation).
The Per Protocol (PP) population will be the primary efficacy analysis population and will include those subjects randomized and without a major protocol deviation.
For quantitative variables summary statistics are the number of values, the mean, standard deviation, median, minimum and maximum values. For qualitative variables, summary statistics are the number of values, the number of missing values, count and percentages for each category.
Data will be presented as number (%), median (range), mean (SD), mean difference (95% CI), OR (95% CI) and RR (95% CI) as appropriate. We will perform analysis of normally distributed continuous variables with t-tests; otherwise we will use a Wilcoxon-Mann-Whitney two sample test.
Consistent with the primary efficacy objective to evaluate the efficacy of 10% Dextrose supplementation to reduce the incidence of neonatal hypoglycaemia as compared to Breast milk alone, the following null hypothesis regarding the primary efficacy endpoint will be tested:
• **H0:** The incidence of hypoglycaemia in subjects treated with supplement of 10% Dextrose along with Breast Milk does not differ from the incidence of hypoglycaemia in subjects treated with Breast Milk alone.
against
• **H1:** The incidence of hypoglycaemia in subjects treated with supplement of 10% Dextrose along with Breast Milk differs from the incidence of hypoglycaemia in subjects treated with Breast Milk alone.
Logistic regression modelling will be used to estimate the odds of hypoglycaemia in the two arms, adjusted for the variables which will be associated with the primary outcome of hypoglicaemia in the univariate analysis on the whole population with a p value < 0.20.
All the Secondary Endpoints will be described in detail using summary statistics, and according to treatment group. 15

Analysis will be performed using EpiInfo (Version 7·2, Centre for Disease Control, Atlanta). All tests comparing the two arms will be two-tailed, and p <0·05 was considered statistically significant.

vital signs for study.pdf

consent form english.pdf

16 **Ethical Considerations**

We consider the intervention of 10% dextrose safe, as it has been used orally for different purposes (analgesic control) and there are no documented adverse effects, its use has also been recommended by international medical agencies (MSF). Further, in terms of glycemic control, there have been a few small trials in the use of oral dextrose that did not find any significant adverse effects (3).

Considering the possibility that giving the baby supplemental feeding may reduce the amount of breast milk, we will encourage continuous breast milk stimulation and monitor time taken to establish feed.

The participants will have their glucose monitored in both arms and a clear rescue plan is elaborated for all participants. The control arm are receiving no less than what low birth weight babies would normally receive in the context (breast milk). Furthermore they will be monitored stringently in terms of glucose levels as well as vital signs.

All patient identifiable data will be removed from the data collection sheets. Data will be stored in a secure space with only researchers having access to it. All data collection sheets are anonymised to ensure patient confidentiality.

The consent form is modelled on the World Health Organisation Consent form. Research staff will provide information to the participant guardians both verbally and in writing (Kiswahili). They will be encouraged to ask questions and discuss any issues. The researchers will be trained in gaining consent and the importance of the individuals right to decline participation in the study. The participant guardians will be given time to consider the proposal and encouraged to discuss with others as well as ask for clarification/ questions if needed. No pressure or coercion will be exerted to participate in the study. No financial incentives or gifts will be offered to participate in the study. Consent will then be obtained in writing- via signature or thumb print. If at any part of the study the participants guardian wish to withdraw from the trial they will be allowed to do so, and routine care will be continued, likewise, If consent is refused, routine care will be offered without prejudice.

Comprehension of the information provided will be assessed using simple questions including "Can you explain to me what you understand so far?" . For patients with disabilities, we will assess capacity to make informed consent and involve relatives where appropriate.