Official Study Title: Detecting Neonataal Hypoglycemia Using Real-Time Continuous Glucose Monitoring (CGM)

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PROTOCOL

TITLE

Detecting Neonatal Hypoglycemia using Real-Time Continuous Glucose Monitoring (CGM)

SUMMARY

Newborn infants have many complex physiological changes taking place that are difficult to anticipate. Infants born to mothers who have diabetes during their pregnancy are especially vulnerable to hypoglycemia. Our study will evaluate blood sugar changes during the first few days of life and the utility of CGM systems to detect clinically significant hypoglycemia in infants. This randomized, controlled single-blind trial will compare infants on CGM alone versus those using CGM who are remotely monitored by a physician through the Dexcom Share application. The number of hypoglycemic events that are detected in each group will be compared. For each time point that the unblinded CGM group has a low blood sugar level, it will be verified by standard heelstick (capillary) measures. Finally, the sensitivity and specificity of detecting hypoglycemia in the infant will also be determined.

INCLUSION CRITERIA

- Participants must be born at 34 weeks gestation or later
- Participants must be admitted Lucile Packard Children's Hospital
- Infants born at outside hospitals and transferred to LPCH will be eligible for the study
- Mothers have a diagnosis of pre-gestational diabetes
- Mothers with gestational diabetes have poorly controlled gestational diabetes defined as elevated Hemoglobin A1c (greater than 6%) during pregnancy or hyperglycemia based on home glucometer readings while pregnant. This includes fasting or pre-prandial blood glucose values of greater than 100 mg/dl, post-prandial blood glucose values greater than 140mg/dl at 1 hour or greater than 120mg/dl at 2 hours consistently.
- Any mothers who require insulin, metformin, or glucose lowering medications during gestation

EXCLUSION CRITERIA

- Infants <2,000g will be excluded from the study.
- If infants receive Acetaminophen, sensor readings will not be included in the analysis for 6 hours after the medication is given because this medication may falsely raise the sensor's glucose readings.
- Infants will also be excluded if they have an anomaly of the skin or subcutaneous tissue that would prevent proper adhesion, placement, and function of the sensor.
- If at any point in time the infant must undergo MRI, CT scan, or diathermy treatment, the sensor, receiver, and transmitter will be removed from the patient completely.

ENROLLMENT PROCEDURES:

- Flyers advertising the study will be posted at the obstetrics clinics at Stanford University.
- Parents of potential participants will be screened remotely for eligibility in the study.
- Every effort will be made to ensure eligible mothers of participants will be recruited and consented by study team members prior to delivery.
- Witnessed telephone consent may be obtained if the family is unable to meet in person.
- The general study, risks, and benefits will be discussed with all potential participants' legal guardians prior to enrollment

STARTING THE DEXCOM CGM: Application

- Participants enrolled in the study will be followed remotely to determine time of delivery of the infant (study participant).
- A trained study team member or staff member will contact the attending physician on call for the newborn to let them know that the participant is enrolled in the study.
- The trained study team member or staff member will come to the infant's bedside and place the Dexcom sensor according to the following steps.
- A Dexcom G4 CGM sensor (Dexcom, San Diego, CA) will be applied using the following steps.
    - After using Standard Precautions, a trained staff member will examine the skin for possible sensor sites.
    - An appropriate area of healthy, in-tact skin will be cleansed and allowed to dry. The sensor will be subcutaneously inserted by trained staff according to the Dexcom user's manual.
    - The transmitter will then be fastened on top of the sensor. The blinded receiver will be kept near the patient to ensure a proper signal as much as possible during the study period.
    - In the remote monitoring group, Dexcom receivers will be blinded to the clinical staff directly caring for the patient by blinding the device using Dexcom Studio. After blinding the receiver, it will be connected to an Ipod that will connect to the Stanford internet. Using the Dexcom Share application installed on the Ipod, the blinded receiver will send glucose data to the Ipod which will remain locked and inaccessible to clinical staff during the study period. The Dexcom Share application will send information to the study physician through the Dexcom Follow application on the study physician's encrypted phone to allow remote monitoring of patients in the experimental group.
    - Using the Dexcom Follow Application, auditory and vibratory alerts will be enabled for blood glucose values <46 mg/dl or signal loss for >60 minutes and sent directly to the study physician remotely monitoring participants.
    - Signal loss of greater than 3 hours will require participants to have a new subcutaneous sensor inserted and the initial calibration steps will need to be repeated.
- Dexcom Receivers and Ipods will remain connected to a power source as much as possible during the study period.

DEXCOM CGM PROTOCOL: Calibration

- After the initial 2 hour start-up period, the sensor will be calibrated using two successive capillary blood glucose measurements using a study glucometer.
- The same type of device will be used for all capillary blood glucose measurements performed on the infant.
- For each capillary blood glucose sample, an area of skin will be cleansed, allowed to dry, pricked using a sterile lancet, and the smallest amount of blood possible will be used for proper testing.
- Every effort will be made to ensure capillary blood glucose levels are checked at least every 12 hours from the time of initial calibration until the time of discharge or 7 days of life, whichever comes first.
- Glucose levels will be entered into the transmitter for calibration within 5 minutes of obtaining the glucose measurement.
- In the remote monitoring group, a trained study staff member will work with nursing staff to perform and input the calibration measurements into the receiver.

MONITORING FOR HYPOGLYCEMIA

- When the monitoring physician receives an alert for a low glucose value <46 mg/dl, they will contact the nurse taking care of the patient. First, the infant will be assessed to see if excess pressure is being placed on the sensor due to positioning. If so, the infant may be repositioned and monitored to see if the glucose values rise above 45mg/dl. If CGM glucose values remain low, a bedside glucose reading will be performed. This value will be recorded in the chart and by the monitoring physician in the study. Based on the standard of care blood glucose reading, the staff will take appropriate measures based on the standard of care (see appendix).
- If the hypoglycemia alarm continues for an additional 60 minutes, the nurse caring for the patient will be prompted to obtain an additional standard of care blood glucose measurement.

    - If the measurement at 60 minutes shows that the patient has a BG >45mg/dl, the CGM may be re-calibrated (see below).
- In the case of severe hypoglycemia (BG <35mg/dl) found in both control and experimental groups during routine calibration procedures will require that the clinical staff caring for the patient be notified to ensure safety of the patient.
- For all blood glucose measurements that are >20% different from the Dexcom CGM values in the experimental group, a blood glucose test may be performed to re-calibrate the sensor prior to the 12 hours. Sensor re-calibration will only occur between glucose values of 40 mg/dl and 400 mg/dl based on manufacturer guidelines.

MONITORING FOR SENSOR SITES FOR INFECTION

- Sensor sites will be assessed at least once per 12 hour nursing shift and as needed during nursing cares for the duration of the study.
- Evidence of inflammation (redness, swelling, discharge) will be documented and discussed with the clinical care and research team.
- If the sensor site is thought to be infected, the sensor will be removed immediately and appropriate steps will be taken to treat the infection by the clinical team managing the patient.

RISKS ASSOCIATED WITH CGM USE

When the needle and sensor are inserted, the child should expect to experience a small amount of pain for a few seconds. After insertion, your child may or may not feel some tenderness or pain.

Pain, inflammation or redness, swelling, minor infection, and minor bleeding at the sensor insertion site are possible risks with your child's use of the study device. In extremely rare cases an infection might spread to other parts of the body. Significant or serious health risks with the investigational device are not anticipated.

Minor irritation may occur where the adhesive pad is placed. This will occur in most research participants and should clear up within hours to not more than a week after removal. The child may experience some itching in the area during the healing process, which is normal. The child may develop an allergic reaction to one or more parts of the sensor and transmitter. This is similar to allergies that occur due to medical tape or jewelry. Allergic reactions will usually be mild and require only a skin cream to make them better. Severe allergic reactions are rare. If the child has an allergic reaction, study staff should be notified.

On rare occasion, the sensor may cause skin injury and tissue trauma known as medical adhesive-related skin injury (MARSI). If this happens, study staff should be notified as soon as possible.

There is a chance that the sensor or needle may break during use of the device. This is not expected to occur; but, if it does, the study staff should be contacted about what to do. They will see if the child has symptoms of infection or inflammation, swelling, redness, or pain at the insertion site. Treatment will be provided if needed. If a sensor breaks, it may be left under the skin indefinitely as long as no portion of the wire sensor fragment is visible above the skin and there are no symptoms of infection, redness, and/or swelling.

The radio waves that the transmitter puts out will not hurt the family or their child, nor will the child be aware of them.

EVALUATION AND TREATMENT OF HYPOGLYCEMIA

- Clinical signs of hypoglycemia will be monitored and documented.
- Hypoglycemic events will be treated using the existing treatment protocol (appendix) and will only be based upon glucometer values

CONTACTING DEXCOM

- Dexcom Technical Support information will be distributed to study personnel and contacted as needed. The contact information is as follows: 1-877-339-2664 and 1-858-200-0200.

DEXCOM CGM REMOVAL

- The CGM will remain in place for 7 days or until the patient is discharged.
- If it is thought that additional value would be gained from continuing use of the CGM for clinical care after 7 days, the CGM may be continued in an unblinded fashion, however the data collected will not be used for the purposes of the study.
- If the sensor should become dislodged at any time during the study period, it will be replaced using the same protocol. However, a new area of healthy skin will be chosen for sensor placement.
- At the end of the study time period, the sensor will be carefully removed by trained staff.
- Skin will be examined carefully and any changes to the skin associated with sensor use will be documented.

DATA ANALYSIS

Data collection

Maternal data, including mother's age, pregnancy history, type of diabetes, and treatment of diabetes during pregnancy were collected. Neonatal characteristics collected included sex, race, ethnicity, gestational age, birth weight, type of delivery, and other risk factors for hypoglycemia. Perinatal stressors were defined as an Apgar score <7, admission to NICU, or treatment of the infant beyond the usual suctioning and stimulating that routinely occurs after birth.14 Prematurity was defined as birth at <37 weeks gestation. Small for gestational age (SGA) infants weighed less than the 10th percentile for gestational age, whereas large for gestational age (LGA) infants weighed greater than the 90th percentile for gestational age.

Power calculation

Using an older retrospective CGM device in a similar cohort of at-risk infants, Harris found that using similar SOC intermittent heel-stick glucose monitoring, 32% of infants had glucose levels <47 mg/dL.15 We estimated that in our cohort, the SOC would find 32% of these high-risk infants with glucose levels <47 mg/dL. We estimated that with a sample size of 40, we should be able to detect a higher CGM rate of hypoglycemia of *57% (80% power, alpha = 0.05, one sided). However, because we were unable to recruit 40 infants during the time frame of the randomized trial, we modified the study design; instead, our goal was to determine if there was additional benefit of using CGM monitoring to detect hypoglycemia missed by SOC testing and to determine the false-positive rate of CGM alerts for hypoglycemia.

Outcome measures

Hypoglycemia was defined as a glucose concentration of <45mg/dL in order to correspond with the hospital's SOC protocol. Primary outcome measures were the number of hypoglycemic events detected by the sensor that were not detected by the hospital SOC. Secondary outcome measures were sensitivity, specificity, and positive predictive value of the device to detect hypoglycemia. When evaluating number of hypoglycemic episodes that occurred with each infant, the start of each hypoglycemic episode needed to be at least 60 minutes from the last episode to allow for treatment and resolution of hypoglycemia. A duration of 60 minutes was used to allow time for breast feeding in accordance with the nursery's SOC procedures (Supplementary Fig. S1). The CGM data were reviewed post hoc using Dexcom Studio Software. Using the Dexcom Studio Software to calculate the average CGM glucose level for each infant, a value of 39 mg/dL was used for all values that were reported as ''low.'' All values reported by the CGM as ''low'' were excluded from the accuracy analysis. The mean absolute relative difference (MARD) was calculated by taking the absolute value of the difference between the CGM and hospital glucometer values and dividing by the hospital glucometer value individually, and then taking the mean of these values.

Additional outcome measures included CGM feasibility in the hospital setting. During the recruitment process and throughout the study, we asked caregivers for feedback about satisfaction with the CGM device. If any devices were removed before the end of the study period, we requested feedback from the families as well.

DATA COLLECTION SCHEDULE

Measurement	Study Entry	Daily	End of Study
Demographics	**X**		
Medical History (mother)	**X**		**X**
Medical History (infant)	**X**		**X**
Chart Review		**X**	**X**
Adverse Events		**X**	**X**
Nutrition		**X**	**X**
Glycemic Trends		**X**	**X**
Exam of skin site/sensor site	**X**	**X**	**X**

APPENDIX:


Glucose Screening and Management of Hypoglycemia in at Risk Asymptomatic Late Preterm and Term Neonate
Initiate feeding within 30-60 minutes of life
Yes
No
Check glucose 30 min after feeding
Check glucose within 1 hr of birth for infants < 37 wks or born to diabetic mothers, and before transfer to F1/F2 for infants found to be SGA when weighed in L&D
< 35 mg/dl
Yes
No
Step 1. If < 25 mg/dl, observe in WBN
Step 2. Feed & check glucose in 1 hr
PATH A
Feed q 2-3 hr and check glucose prior to feedings
< 25 mg/dl
25 to 34 mg/dl
≥ 35 mg/dl
< 45 mg/dl
≥ 45 mg/dl
Notify physician & Send glucose to lab
1) Notify Physician 2) Re-feed & check glucose in 1hr
GO TO PATH A
Re-feed & check glucose in 1 hr
< 35 mg/dl
≥ 35 mg/dl
< 35 mg/dl
35 to 44 mg/dl**
≥ 45 mg/dl
GO TO PATH A
** Notify physician after 2 re-feed attempts
GO TO PATH A
Feed = 1) breastfeed OR 2) 5 to 10ml formula or donor human milk
No further glucose checks necessary after glucose ≥ 45 mg/dl x 3 (exception: Late Preterm and SGA need additional glucose check at 24 hours of life with bilirubin or newborn screen testing)