GLUCOSE GEL AS A TREATMENT FOR NEONATAL HYPOGLYCEMIA

by

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DISSERTATION

Submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy in Nursing

University of Texas at Arlington

August 2021

Arlington, Texas

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ACKNOWLEDGEMENTS

The study reported in the second manuscript was supported by a grant from the University of Texas at Arlington Center for Research and Scholarship. Additional funding was provided by the University of Texas at Arlington Bone-Muscle Research Center.

ABSTRACT

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The University of Texas at Arlington, 2021

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This article-based dissertation consists of two complete manuscripts related to oral glucose gel, which is used to treat neonatal hypoglycemia (NH). In the first manuscript, a pre and post-intervention retrospective study was completed to examine the effects of the introduction of glucose gel on the exclusive breastfeeding rate and the admission rate to the neonatal intensive care unit (NICU) on neonates over 35 weeks gestation who were at risk for NH in a mother-baby unit of a Baby-Friendly hospital. There were 198 newborns in the pre-intervention sample and 203 in the post-intervention sample. The exclusive breastfeeding rates in the pre-intervention group were similar to those of the post-intervention group (56.6% of 198 vs. 59.1% of 203, $p = .62$), as were the NICU admission rates for NH (2.5% of 198 vs. 1.5% of 203, $p = .50$). In our suburban, Baby-Friendly mother-baby unit, the introduction of glucose gel did not significantly impact the exclusive breastfeeding or NICU admission rates.

The second manuscript contains the results of a laboratory study that measured glucose concentrations both within and among tubes in the two brands of oral glucose gel that are used in the United States, Glutose 15™ and Insta-Glucose™. We found that glucose is not uniformly distributed through the tubes with an observed percent

difference between the 3 sections of a Glutose 15™ tube of 12.3- 53.8% and between the 3 sections of an Insta-Glucose™ tube of 40.7- 79.6%. The difference in concentration of glucose between whole tubes of 3 lots of Glutose 15™ was 1.6% and between 3 lots of Insta-Glucose™ was 8.8%. This lack of consistency may account for the mixed results in the literature about the effectiveness of oral glucose gel as a treatment for NH.

The dissertation concludes with a discussion, limitations, implications for nursing practice, and areas for future research.

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Glucose Gel as a Treatment for Neonatal Hypoglycemia

CHAPTER 1

INTRODUCTION

Oral glucose gel is used to treat neonatal hypoglycemia (NH), an important health issue for newborns. None of the early studies on the use of gel for NH were conducted in a Baby-Friendly hospital in the United States. Mixed results in the literature about the effectiveness of the gel may be because commercially available oral glucose gel was designed for adults and may provide inconsistent doses of glucose both between and among different tubes of gel. What follows is a discussion of the background and significance of NH, a description of a physiology-based theoretical framework designed to help understand blood glucose regulation in newborns, and the rationale for two manuscripts. The rationale for Manuscript One, a study of the effects of glucose gel on newborns at risk for neonatal hypoglycemia in a Baby-Friendly hospital, will include the research questions and limitations of the study. The rationale for Manuscript Two, a laboratory experiment to test glucose concentrations in the two most widely-used brands of glucose gel in the United States, Glutose 15™ (Paddock Laboratories, Minneapolis, MN) and Insta-Glucose™ (Bausch Health, Laval, Quebec), will include background and the research questions.

Background and Significance

While still in utero, a fetus receives the glucose required for energy and growth from the maternal circulation intravenously through the placenta (Harding et al., 2017). At birth, the infant's blood glucose levels fall as the exogenous maternal glucose supply is interrupted (Hawdon, 2015). One of the primary physiological challenges a newborn experiences during transition to extrauterine life is maintenance of blood glucose (Hay et al., 2009). NH is a blood

glucose level low enough that delivery to critical organs, such as the brain, is compromised (Cornblath et al., 2000). NH is significant because prolonged and severe episodes of NH are associated with neurological injury (Hawdon et al., 2017). Treatment for NH in the United States costs approximately 2.1 billion dollars each year (Rawat et al., 2016).

Approximately 30% of otherwise well newborns have risk factors for NH at birth and require blood glucose screening (Makker et al., 2018). Infants are considered at risk for NH if they are born late preterm (between 34-37 weeks gestation), small for gestational age (SGA) (at a birth weight less than the 10th percentile), large for gestational age (LGA) (at a birth weight greater than the 90th percentile), or if their mothers are diabetic (Hosagasi et al., 2018).

Treatments for NH

The most common treatment for NH is formula feeding. However, this may interfere with normal metabolic adaptation of ketogenesis and gluconeogenesis (Chiruvolu et al., 2017). Formula feeding is associated with early cow's milk protein exposure and reduced insulin sensitivity, predisposing infants to Type 1 and Type 2 diabetes respectively (Manco et al., 2011). In addition, it may interfere with the establishment and duration of breastfeeding and may increase the infant's risk of infection and allergies by changing the natural gut microbiome (Harding et al., 2017). If treatment with formula feeding is unsuccessful in stabilizing blood glucose values, infants are often transferred to the neonatal intensive care unit (NICU) for intravenous (IV) dextrose infusions. This is also problematic because it results in separation of infants and mothers, which may interrupt breastfeeding and bonding (Rawat et al., 2016).

Glucose gel effects on glycemic control

Oral glucose gel is a relatively new treatment for NH. In a benchmark randomized, double-blinded, placebo-controlled trial, which included 242 newborns from New Zealand,

Harris, Weston, Signal, Chase, and Harding (2013) found that administering the gel was more effective in maintaining adequate blood glucose control (interstitial blood glucose concentrations of 2.6 mmol/L or more up to 48 hours after birth) than a placebo. Though they did not explicitly state it in their manuscript, the oral gel used in this study was compounded in the hospital's pharmacy (Harding, J.E., personal communication, December 15, 2019). From Australia, Barber et al. (2018) compared 36 newborns with NH who were treated with Glutose 15™ glucose gel to 24 newborns with NH who were treated with formula. They defined the treatment as successful if the newborn had a blood glucose of 46.8 mg/dL (Barber et al., 2018). The mean blood glucose value reached the treatment success benchmark in both groups, but the mean was higher ($p = 0.07$) in the formula group after the first treatment and was significantly higher ($p = 0.003$) in the formula group after the second treatment (Barber et al., 2018). Gregory et al. (2019) in the United States used Glutose 15™ in their retrospective pre and post-cohort study of 2688 asymptomatic newborns who were tested for NH (Rostas, S., personal communication, April 19, 2021). They found that exclusively breastfed neonates and unfed neonates had similar increases in blood glucose values after the first but not second dose of gel (Gregory et al., 2019).

Glucose gel effects on NICU admissions for NH

Multiple research teams in New Zealand, Australia, and the United States have reported that infants with NH who were treated with glucose gel were less likely to be admitted to the NICU. In the only placebo-controlled study, Harris et al. (2013) found that infants who were given glucose gel were less likely ($p = 0.03$) than infants given placebo gel to be admitted to the NICU for NH with 14% of the infants treated with glucose gel admitted to the NICU and 25% of the infants given the placebo admitted to the NICU for NH. The other reports about glucose gel and NICU admissions were reports of pre and post-intervention studies. They showed a wide

range in NICU admission rate difference from 2.0%-73%. Rawat et al. (2016) conducted a retrospective chart review study in New York after including Glutose 15™ glucose gel into their NH treatment protocol. They included 248 infants in the pre-gel arm of the study and 250 infants in the post-gel arm (Rawat et al., 2016). After implementation of glucose gel, they reported a significant decrease in admission to the NICU for NH from 42% to 26% ($p < 0.01$). In Illinois, another group also reported on introduction of Glutose 15™ glucose gel into a NH protocol and its effectiveness in reducing NICU admissions for NH (Bennett et al., 2016). Their study included 870 newborns in the pre-gel arm of the study and 1,089 newborns in the post-gel arm of the study. They found their treatment protocol was associated with a 73% reduction in admissions to NICU for NH. In Australia, Ter et al. (2017) used a convenience sample to audit the health records of 200 sequential newborns and found that the use of Glutose 15™ glucose gel resulted in a significant reduction ($p = 0.01$) in admissions to the NICU for hypoglycemia from 29% to 14%. Makker et al. (2018) reported the results of a non-randomized, uncontrolled study in Florida with 421 babies in the pre-gel arm of the study and 383 babies in the post-gel arm. They did not report the brand of gel they used. They reported that introduction of glucose gel was associated with a significant decrease in the NICU admission rate from 8% to 4% ($p = 0.01$). In Boston, Gregory et al. (2020) noted a decrease in NICU admission for intravenous dextrose administration from 8.6% to 5.6% ($p = 0.005$) after the introduction of Glutose 15™.

Contrastingly, in Australia, Gibson et al. (2020) compared 29 neonates with NH in a group before the implementation of Glutose 15™ to a group of 35 in the post-intervention group and found that the decrease in NICU admission rate from 13.8% to 11.4% was not significant ($p = 0.534$) (Gibson et al., 2020; Gibson, B.L., personal communication, April 23, 2021). Ponnapakkam et al. (2020) compared 214 newborns at risk for NH before the implementation of

Glutose 15™ to 293 newborns at risk for NH after implementation and found no significant difference in NICU admission rates with a 13% NICU admission rate in the pre-implementation group and a 14% NICU admission rate in the post-implementation group (Ponnapakkam et al., 2020, Ponnapakkam, A. personal communication, April 22, 2021).

Glucose gel effects on exclusive breastfeeding rates

In addition to investigating whether glucose gel is effective in reducing the NICU admissions for NH, researchers have also reported on the effectiveness of glucose gel in increasing the exclusive breastfeeding rate in infants with NH. In New Zealand, Harris et al. (2013) found that babies in the pharmacy-compounded glucose gel group received significantly less expressed breastmilk (2.4 mL/ kg vs. 4.7 mL/ kg, $p = 0.03$) and fewer formula feedings (7 vs. 10, $p = 0.04$) (although not less volume) than babies in the placebo group. They did not report an exclusive breastfeeding rate at hospital discharge. Rawat et al. (2016) reported that introduction of Glutose 15™ into the hospital's NH protocol was associated with a significant increase ($p = 0.03$) in the exclusive breastfeeding rate at discharge from 19% of the infants with NH to 28%. Bennett et al. (2016) reported an increase in exclusive breastfeeding at discharge from 0% to 49% for the infants of mothers who intended to exclusively breastfeed. Makker et al. (2018) also reported that glucose gel was associated with an increase ($p < 0.001$) in exclusive breastfeeding at discharge from 6% to 19% for the infants of mothers who intended to exclusively breastfeed. There were other variables, such as increased staff breastfeeding education and lactation support which may have confounded these breastfeeding results. Gibson et al. (2020) reported a significant increase in the exclusive breastfeeding rate from 20.7% to 54.3% ($p = 0.10$) after the incorporation of Glutose 15™ into the NH protocol. Divergently,

Ponnapakkam et al. (2020) reported no significant change in the exclusive breastfeeding rate after implementing Glutose 15™.

Theoretical Framework

Textbook authors delineate the physiology of neonatal blood glucose regulation, but no one has created a theoretical framework to serve as a model. We do know that insulin from the pancreas leads to cellular glucose intake and lowering of blood glucose levels (McCance et al., 2014). Glucagon is an insulin antagonist that is released from the pancreas and works on glycogen stores in the liver to release glucose into the bloodstream, thereby increasing blood glucose levels (McCance et al., 2014). Fetuses are unable to produce their own glucose and receive all their blood glucose from their mothers (Martin et al., 2020). They do secrete their own insulin and form their own hepatic glycogen store (Martin et al., 2020). At birth, blood glucose levels in neonates fall when the exogenous maternal glucose supply is stopped (Hawdon, 2015). Newborns then rely on feeding and mobilization of hepatic glycogen to help sustain blood glucose concentrations within 30 to 90 minutes after a baby's birth (Flannigan, 2011; Martin et al., 2020). Then, the levels rise in healthy infants and remain at a normal level of 40 to 80 mg/dL (Martin et al., 2020). However, this mobilization of hepatic glycogen is dependent on the enzyme glycogen-6-phosphatase, which is found in low levels in neonates and increases to adult levels within a few days (Flannigan, 2011). In the meantime, the neonatal body exhibits an endocrine stress response involving insulin and glucagon to break down glycogen in the liver to blood glucose (Flannigan, 2011).

Although this physiology is well-described in textbooks and physiology papers, none of the research articles on neonatal hypoglycemia refer to a model of glucose regulation. Because theoretical frameworks help to ground and guide research, a model is needed to describe what is

believed to be involved in blood glucose regulation. I developed the model of Neonatal Blood Glucose Regulation in 2020 to examine how blood glucose is regulated in neonates (Appendix A). Even though most of the research on neonatal blood glucose regulation involves examining hypoglycemia and restoring normal blood glucose values, a complete model of blood glucose regulation necessarily includes hyperglycemia.

The Rationale for Manuscript One

The Baby-Friendly Hospital Initiative (BFHI) is a global effort to improve the care of pregnant women, mothers, and newborns at health facilities that provide maternity services by protecting, promoting, and supporting breastfeeding (World Health Organization, 2019). The study site was designated a Baby-Friendly Hospital in 2017 after extensive staff and parent education and practice changes that included early initiation of breastfeeding and prolonged skin-to-skin contact between mothers and newborns. With implementation of these core Baby-Friendly processes, the study site's overall rate of exclusive breastfeeding at discharge increased 24% in neonates at risk for NH (from 45.7% in 2015 to 56.6% in 2017). Additionally, the NICU admission rate for NH remained low (2.5% in 2017). The purpose of the study reported in Manuscript One was to describe the effects of the introduction of Glutose 15™ gel to the NH protocol on exclusive breastfeeding rates at discharge and NICU admission rates among clinically-well newborns born at 35 weeks gestation or greater who were at risk for NH in a Baby-Friendly hospital.

Research Questions for Manuscript One

1. For infants at risk for NH in a mother-baby unit, how will introduction of glucose gel into the NH protocol affect the exclusive breastfeeding rate at discharge?

2. For infants at risk for NH in a mother-baby unit, how will introduction of glucose gel into the NH protocol affect the rate of admission to NICU?
3. For infants at risk for NH in a mother-baby unit, how will introduction of glucose gel into the NH protocol affect the number of dextrose gel boluses given?

Limitations of Manuscript One

1. This was a retrospective cohort study. Therefore, confounding variables may have affected the results.
2. Though no significant differences between key demographics or clinical variables were noted between the two cohorts, a matched pair cohort design would have allowed for more generalization of results.
3. This was a single-site study and external validity may be limited because the population served at the suburban hospital may not represent all newborns at risk for NH.
4. Inconsistencies in glucose dosing in Glutose 15™ may have confounded results.

The Rationale for Manuscript Two

One reason for the mixed results in the efficacy of glucose gel could be inconsistencies in the dosage of glucose found in commercially available oral glucose gel. A research group from Canada reported that the glucose content in a tube of commercially available glucose gel can vary by as much as 81% between batches and in doses tested from different areas of the tube (Solimano, Kwan, Osiovich, Dyer, & Elango, 2018). Therefore, an infant given the same volume of glucose gel from the first section of the tube may not receive the same dose of glucose as an infant receiving gel from the end of the tube. The authors in the original benchmark study used a gel that was compounded in the hospital's pharmacy for the study (Harding, J.E., personal communication, December 15, 2019). Subsequent researchers used commercially available oral

gels that were originally intended for adult diabetics experiencing hypoglycemia. An adult would take an entire tube as a dose, but for newborns, approximately 11 doses are abstracted from a single tube (Trickey, S.P., November 19, 2019). Therefore, consistency of glucose in aliquots extracted from the different parts of the same tube calls into question the validity and generalizability of reported outcomes. Because these products are over-the-counter and not prescription, the manufacturers are not required to do consistency studies (Smith, K.J, personal communication, November 3, 2019). There are no published studies on consistency of glucose gel concentrations in the brands commonly used in the United States. The study reported in Manuscript Two was designed to fill this gap in the literature by studying the consistency in the two most-commonly used oral glucose gels in the United States, Glutose 15™ (Paddock Laboratories, Minneapolis, MN) and Insta-Glucose™ (Bausch Health, Laval, Quebec).

Research Questions for Manuscript Two

1. Is there a difference in the glucose concentrations in aliquots taken from different areas of Glutose 15™ and Insta-Glucose™ oral glucose gel tubes?
2. Is there a difference in the glucose concentrations in aliquots taken from different batches of Glutose 15™ and Insta-Glucose™ oral glucose gel tubes?

Limitations of Manuscript Two

1. This study is a laboratory study and the actual methods pharmacists at hospitals use to collect individual glucose gel doses may vary. While the pharmacists at some hospitals draw the gel directly from the tube into syringes, others express all the gel into a different container before drawing it into syringes. These different methods could produce different results than this laboratory study.

2. The laboratory is only tested for glucose. Other carbohydrates could be present in the gel and this could have some clinical significance.

Summary

NH is a significant health problem. Traditional treatments like formula feeding breastfed babies and transferring babies with NH to the NICU for IV dextrose infusions are not benign interventions. Clinicians are increasingly using oral glucose gel as a treatment for NH with the intention of maintaining a neonate's blood glucose levels while supporting exclusive breastfeeding and mother-newborn bonding. However, little is known about the use of oral glucose gel in a Baby-Friendly mother-baby unit with already high exclusive breastfeeding rates and low NICU admission rates. Additionally, the previous studies upon which the value of oral glucose gel has been based used a hospital-compounded oral glucose gel, not the commercially available oral glucose gels designed as adult diabetic care products that hospitals in the United States are using. There is no research on the consistency of dosing in these products in the United States. Publishing the results of studies on the use of oral glucose gel in a Baby-Friendly mother-baby unit and on the consistency of glucose gel concentrations in commercially available oral glucose gel in the United States can ultimately lead to better treatment and outcomes for newborns with NH.

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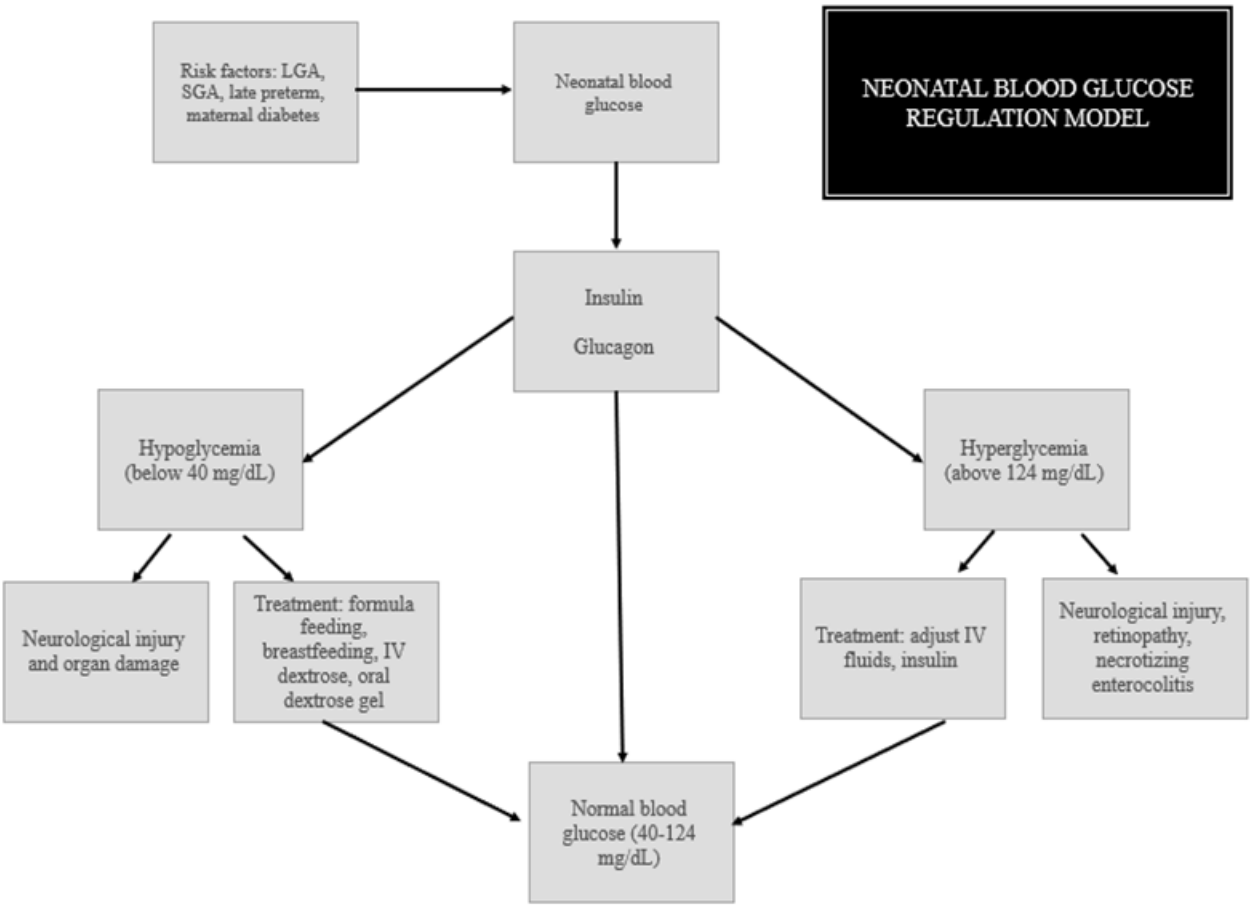
Appendix A

Neonatal Blood Glucose Regulation Model



Glucose Gel as a Treatment for Neonatal Hypoglycemia

CHAPTER 2

EFFECTS OF DEXTROSE GEL IN NEWBORNS AT RISK FOR NEONATAL HYPOGLYCEMIA IN A BABY-FRIENDLY HOSPITAL[1]

Stanzo, K., Desai, S., & Chiruvolu, A. (2020). Effects of dextrose gel in newborns at risk for neonatal hypoglycemia in a Baby-Friendly hospital. *Journal of Obstetric, Gynecologic & Neonatal Nursing*, *49*(1), 55–64. https://doi.org/10.1016/j.jogn.2019.11.006

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RESEARCH

Effects of Dextrose Gel in Newborns at Risk for Neonatal Hypoglycemia in a Baby-Friendly Hospital

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Keywords
Baby-Friendly
blood glucose
blood sugar
breastfeeding
dextrose gel
glucose gel
neonatal hypoglycemia

ABSTRACT

Objective: To describe the effects of the introduction of dextrose gel to the neonatal hypoglycemia (NH) protocol on exclusive breastfeeding rates at discharge and NICU admission rates among clinically well newborns born at 35 weeks gestation or greater who were at risk for NH in a Baby-Friendly hospital.

Design: Quasi-experimental, pre- and postintervention.

Setting: A suburban, Baby-Friendly hospital with approximately 2,000 births annually.

Participants: Clinically well newborns born at 35 weeks gestation or greater at risk for NH who were admitted to the mother–baby unit.

Methods: We compared 198 newborns at risk for NH born in the 6-month period before the introduction of dextrose gel (November 15, 2016, through May 14, 2017) versus 203 newborns born in the 6-month period after the introduction (May 15, 2017, through November 14, 2017). In the preintervention group, the NH protocol included blood glucose monitoring, prolonged skin-to-skin contact, feeding, and dextrose administered intravenously. In the postintervention group, oral dextrose gel was added to the NH protocol.

Results: We found no differences in maternal or newborn characteristics between the pre- and postintervention groups. Dextrose gel was given to 50 newborns (approximately 25%) of 203 in the postintervention group. The proportion of newborns who were exclusively breastfed at discharge was similar between groups (56.6% of 198 vs. 59.1% of 203, $p = .62$), as were the NICU admission rates for hypoglycemia (2.5% of 198 vs. 1.5% of 203, $p = .50$).

Conclusions: In a suburban Baby-Friendly hospital, introduction of dextrose gel into the NH protocol had no significant effect on exclusive breastfeeding at discharge or NICU admission rates.

JOGNN, 49, 55–64; 2020. https://doi.org/10.1016/j.jogn.2019.11.005

Accepted November 2019

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(Continued)

The authors report no conflict of interest or relevant financial relationships.

While still in utero, a fetus receives the glucose required for energy and growth from the mother's blood through the placenta (Harding, Harris, Hegarty, Alsweiler, & McKinlay, 2017). When separated from the mother at birth, the newborn's blood glucose level falls (Hawdon, 2015). One of the primary physiologic challenges a newborn experiences during the transition to extrauterine life is maintenance of a healthy blood glucose level (Hay, Raju, Higgins, Kaihan, & Devaskar, 2009).

Neonatal hypoglycemia (NH) occurs when the blood glucose level falls so low that critical organs, such as the brain, are compromised. Prolonged and severe episodes of NH are associated with neurologic injury (Hawdon, Beer, Sharp, & Upton, 2017). The exact range of blood glucose concentration associated with poor neurodevelopmental outcomes is unknown, partly because of individual differences in alternative fuels, such as ketone bodies and lactate, that newborns produce in response to NH (Adamkin, 2011). The currently understood physiology of neonatal blood glucose regulation served as the theoretical framework for our study (Polin, Fox, & Abman, 2010). The American Academy of Pediatrics recommends a threshold of plasma glucose levels less than 40 mg/dL to treat for hypoglycemia in the first 4 hours of life and less than 45 mg/dL thereafter (Hosagasi, Aydin, Zencironglu, & Ustun, 2018). In a large cohort of newborns, NH was not associated with adverse neurologic outcomes when treatment was

Breastfed newborns who are at risk for hypoglycemia are often given supplemental formula or separated from their parents, and these interventions impede normal metabolic adaptation.

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provided to maintain a blood glucose concentration of at least 47 mg/dL (McKinlay et al., 2015).

Determining the precise incidence of NH in the United States is difficult because different glucose ranges have been used to define NH in the published literature. Approximately 30% of otherwise well newborns have risk factors for NH at birth and require blood glucose screening (Makker et al., 2018). In a previous study at our hospital, 15.2% of clinically well neonates had at least one risk factor for NH, and 50% of them experienced NH (Chiruvolu et al., 2017). Newborns are considered at risk for NH if they are born late preterm (between 34 and 37 weeks gestation), are small for gestational age (SGA; birth weight less than the 10th percentile), or are large for gestational age (LGA; birth weight greater than the 90th percentile) or if their mothers have diabetes (Hosagasi et al., 2018).

The most common treatment for NH is formula-feeding. However, this may interfere with normal metabolic adaptation of ketogenesis and gluconeogenesis (Chiruvolu et al., 2017). Formula-feeding is associated with early cow's milk protein exposure and reduced insulin sensitivity, which predispose newborns to Type 1 and Type 2 diabetes, respectively (Manco et al., 2011). In addition, formula-feeding may interfere with the establishment and duration of breastfeeding and may increase the newborn's risk of infection and allergies by changing the natural gut microbiome (Harding et al., 2017). If treatment with formula-feeding does not stabilize blood glucose values, newborns are often transferred to the NICU for intravenous (IV) dextrose infusions. This is also problematic because it results in separation of newborns and mothers, which may interrupt breastfeeding and bonding (Rawat et al., 2016).

Oral dextrose gel is a relatively new treatment for NH. In a benchmark randomized, double-blind, placebo-controlled trial that included 242 newborns in New Zealand, Harris, Weston, Signal, Chase, and Harding (2013) found that administering the gel was more effective to maintain adequate blood glucose control (interstitial blood glucose concentrations of 2.6 mmol/L or more up to 48 hours after birth) than placebo. In that study, researchers measured blood glucose values through heel lances and subcutaneously continuous blood glucose monitors (Harris et al., 2013).

Multiple research teams have reported on the use of dextrose gel to increase the exclusive breastfeeding rate in newborns with NH. In New Zealand, Harris et al. (2013) found that newborns in the dextrose gel group received significantly less expressed breast milk (2.4 mL/kg vs. 4.7 mL/kg, $p = .03$) and fewer formula feedings (7 vs. 10, $p = .04$), although not less volume, than newborns in the placebo group. They did not report an exclusive breastfeeding rate at hospital discharge. Rawat et al. (2016) reported that introduction of dextrose gel to the hospital's NH protocol was associated with a significant increase ($p = .03$) in the exclusive breastfeeding rate at discharge from 19% to 28%. Bennett, Fagan, Chaharbakhshi, Zamfirova, and Flicker (2016) reported an increase in exclusive breastfeeding at discharge from 0% to 49% for newborns at risk for NH whose mothers intended to exclusively breastfeed. Makker et al. (2018) also reported that dextrose gel was associated with an increase ($p < .001$) in exclusive breastfeeding at discharge from 6% to 19% for the newborns of mothers who intended to exclusively breastfeed. Variables, such as increased education about breastfeeding for staff members and lactation support for mothers may have confounded the results of these studies. In addition, one research group reported that the dextrose content in a tube of dextrose gel can vary by as much as 81% between batches and within the same tube (Solimano, Kwan, Osiovich, Dyer, & Elango, 2018). Therefore, the same volume of dextrose gel from the first section of the tube may not include the same dose of dextrose as the same volume of gel from the end of the tube.

Multiple research teams in New Zealand, Australia, and the United States have reported that newborns with NH who were treated with dextrose gel were less likely to be admitted to the NICU. In the only placebo-controlled study, Harris et al. (2013) reported that 14% of the newborns treated with dextrose gel were admitted to the NICU for NH versus 25% of the newborns given the placebo. Other reports of pre- and post-intervention studies with dextrose gel showed reductions in NICU admission rates from 4% to 16%. Rawat et al. (2016) conducted a retrospective chart review in New York after including

dextrose gel in the NH treatment protocol. They included 248 newborns in the preintervention arm of the study and 250 newborns in the postintervention arm (Rawat et al., 2016) and reported a significant absolute decrease in admission to the NICU for NH from 42% to 26% ($p < .01$). Similarly. in Illinois, Bennett et al. (2016) included 870 newborns in the preintervention arm and 1,089 newborns in the postintervention arm of their study. The use of dextrose gel was associated with a 7.7% absolute reduction in admissions to the NICU for NH. In Australia, Ter, Halibullah, Leung, and Jacobs (2017) used a convenience sample to audit the health records of 200 newborns born sequentially and found that the use of dextrose gel resulted in a significant absolute reduction ($p = .01$) in admissions to the NICU for hypoglycemia from 29% to 14%. Makker et al. (2018) reported the results of a nonrandomized, uncontrolled study in Florida with 421 newborns in the preimplantation arm of the study and 383 newborns in the postimplementation arm. The introduction of dextrose gel was associated with a significant absolute decrease in the NICU admission rate from 8% to 4% ($p = .01$).

None of these studies was conducted with newborns who were born in Baby-Friendly hospitals in the United States. In addition, the facilities in all of these studies had lower baseline rates of exclusive breastfeeding at discharge and greater baseline rates of NICU admissions for hypoglycemia than our facility, which is Baby-Friendly designated. For example, among newborns at risk for NH, our baseline exclusive breastfeeding rate was 56.6%, but Rawat et al. (2016) reported a 19% exclusive breastfeeding rate, and Makker et al. (2018) reported 6%. Bennet et al. (2016) and Ter et al. (2017) did not report baseline exclusive breastfeeding rates. Our hospital had a baseline NICU admission rate for NH of 2.5%, but Rawat et al. (2016) reported a rate of 42%, Bennett et al. (2016) reported a rate of 10.6%, Ter et al. (2017) reported a rate of 29%, and Makker et al. (2018) reported a rate of 8.1%.

Our hospital is a community, suburban institution that opened in 2012. The hospital's interprofessional breastfeeding committee undertook a series of educational and quality improvement projects that resulted in an increase in the exclusive breastfeeding rate for all term, singleton, non-NICU newborns at hospital discharge from 39% of a random sample that included 109 newborns in 2012 to 77% of a random sample that included 376 newborns in 2016. Our sample was smaller in 2012 because the hospital opened midyear. After a prolonged (12–24 hours) skin-to-skin care intervention, the exclusive breastfeeding rates at discharge for newborns at risk for NH increased from 36.4% of 272 to 45.7% of 289 ($p = .074$), and NICU admission rates significantly decreased from 8.1% of 272 to 3.5% of 289 ($p = .018$; Chiruvolu et al., 2017).

The hospital was designated Baby-Friendly in May 2017. The Baby-Friendly Hospital Initiative is a global effort to improve the care of pregnant women, mothers, and newborns at health facilities that provide maternity services through the protection, promotion, and support of breastfeeding (World Health Organization, 2019). During the preparation for Baby-Friendly designation, our staff and parents participated in extensive education about the expression of colostrum, early initiation of breastfeeding, and prolonged skin-to-skin care. With the implementation of these core Baby-Friendly processes, our committee noted an increase in the overall rate of exclusive breastfeeding at discharge and a 24% improvement in exclusive breastfeeding rates in newborns at risk for NH (from 45.7% in 2015 to 56.6% in 2017). In addition, our NICU admission rate for NH remained low (2.5% in 2017). We introduced dextrose gel into the NH protocol to further increase the exclusive breastfeeding rates at discharge and help the natural metabolic adaptation of newborns at risk for NH.

The purpose of our study was to describe the effects of the introduction of dextrose gel to the NH protocol on exclusive breastfeeding rates at discharge and NICU admission rates among clinically well neonates born at 35 weeks gestation or greater who were at risk for NH in a Baby-Friendly hospital. We hypothesized that the proportion of newborns at risk for NH who exclusively breastfed at discharge would increase by at least 20% without affecting the low NICU admission rate. We set a goal of a 20% increase based on the increases we noted after the prolonged skin-to-skin care intervention and introduction of Baby-Friendly processes.

Methods

Design

This was a 1-year, quasi-experimental, pre- and postintervention study to retrospectively compare two cohorts: newborns at risk for NH born before implementation of a dextrose gel

The introduction of dextrose gel did not improve exclusive breastfeeding rates at discharge or decrease NICU admission rates for newborns at risk for hypoglycemia in a Baby-Friendly hospital.

intervention (November 15, 2016, through May 14, 2017) and newborns at risk for NH born after implementation of the intervention (May 15, 2017, through November 14, 2017). In the pre-intervention group, the NH protocol included blood glucose monitoring, prolonged skin-to-skin contact, feeding, and IV dextrose. In the postintervention group, the NH protocol also included oral dextrose gel. The NH protocol, with highlighted changes introduced in the postintervention period, is presented in Figure 1. We prepared this article based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting cohort studies (Sharp, Poulaliou, Thompson, White, & Wood, 2014).

Setting

Our study was conducted at a 143-bed, full-service, acute care, suburban hospital with approximately 2,000 births annually. Clinically well newborns born at 35 weeks gestation or later are admitted to the mother–baby unit; those born at less than 35 weeks gestation are directly admitted to the Level III NICU per hospital policy.

Participants

Participants included otherwise healthy newborns born at 35 weeks gestation or later who were at risk for NH and were admitted to the mother–baby unit in the 6-month periods before and after the implementation of dextrose gel in the NH protocol. Newborns were considered at risk for NH if they were SGA, LGA, late preterm, or born to women with diabetes.

Procedure

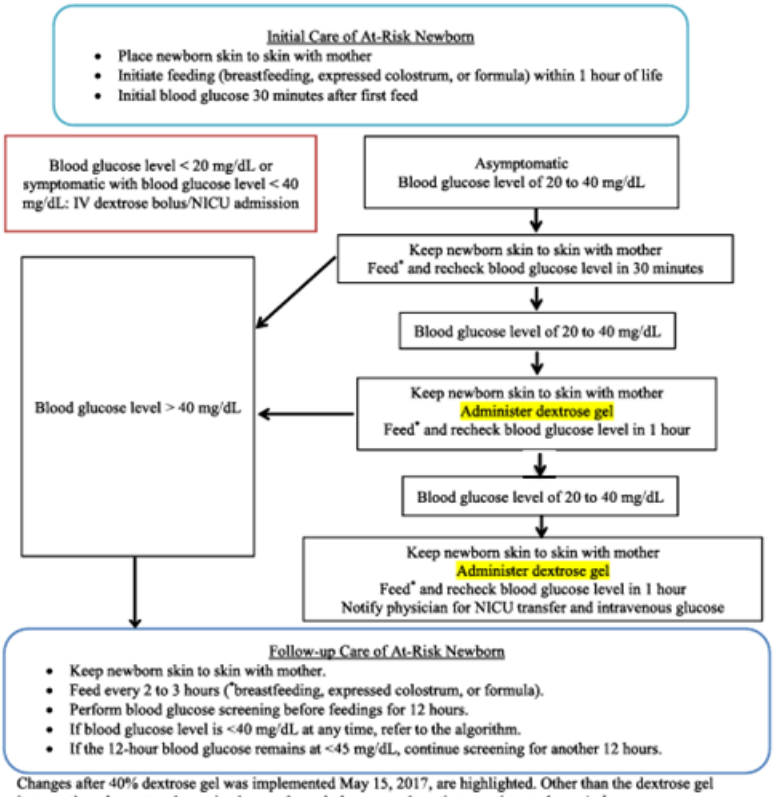
Per the NH protocol (see Figure 1), newborns at risk for NH in the pre- and postintervention groups were to be placed prone on their mothers' bare chests immediately after birth following all vaginal and uncomplicated cesarean births. Feeding was initiated within the first hour, and blood glucose monitoring began 30 minutes after the first feeding. Nurses encouraged women to keep their newborns skin to skin until blood glucose monitoring was completed in accordance with the NH protocol. For most newborns, the period of blood glucose monitoring was 12 hours. However, if the 12-hour blood glucose level was less than 45 mg/dL, the blood glucose monitoring and skin-to-skin contact were continued for an additional 12 hours.

While the newborn was skin to skin with the mother, a clinical nurse collected blood glucose samples by heel stick before each feeding. The nurse then analyzed the sample immediately with the precision-Xceed Pro (Abbott Diabetes Care, Alameda, CA) point-of-care glucometer using compatible blood glucose strips. Newborns were admitted to the NICU if they were symptomatic with a blood glucose level of less than 40 mg/dL, or if the blood glucose level was less than 20 mg/dL without symptoms, or if the blood glucose level remained at less than 40 mg/dL despite receiving one IV dextrose bolus in the mother–baby unit.

In the postintervention group, the only change to the NH protocol was the addition of oral dextrose gel. No other changes, such as new policies or staff changes, were implemented during the study period. When dextrose gel was required, nurses used gauze to dry the newborn's mouth and then massaged 0.5 mL/kg of Glutose 15 (Paddock Laboratories, Inc., Minneapolis, MN) lemon-flavored 40% oral dextrose gel into the buccal mucosa. If the newborn was asymptomatic and the blood glucose level was between 20 and 40 mg/dL, nurses helped parents feed their newborn according to the parents' feeding choice, and skin-to-skin care was continued. A nurse then rechecked the blood glucose level in 30 minutes. If the blood glucose level remained at 20 to 40 mg/dL, the nurse administered dextrose gel, helped the parents feed the newborn again (by breastfeeding, feeding expressed breast milk, or feeding formula), and then rechecked the blood glucose level 1 hour after the administration of dextrose gel. If the blood glucose remained at less than 40 mg/dL despite two doses, the newborn was transferred to the NICU for IV dextrose infusion.

Data Analysis

We used a convenience sample of approximately 200 newborns in each arm of the study. The sample size was based on feasibility, given that approximately 2,000 newborns are born in our hospital each year and approximately 15% are at risk for NH. We collected all descriptive variables that could influence the incidence of NH through medical record review. The maternal variables included demographic information, obstetric complications, and birth variables. The neonatal variables included gestational age, birth weight, sex, and Apgar scores.



Changes after 40% dextrose gel was implemented May 15, 2017, are highlighted. Other than the dextrose gel intervention, the protocol remained same through the pre- and postintervention study periods.

Figure 1. Screening and management of postnatal glucose homeostasis in late preterm or term newborns at risk for neonatal hypoglycemia.

We calculated the proportions of newborns born late preterm or born to mothers with diabetes. We defined *late prematurity* as 35 to 36 6/7 weeks gestation by best estimate. We categorized the diagnosis of diabetes from prenatal records as Type 1 or Type 2 (diagnosed before pregnancy) or gestational diabetes (diagnosed during pregnancy by oral glucose tolerance testing). We also calculated the proportion of newborns born SGA or LGA. We defined *SGA* as less than the 10th percentile for gestational age and *LGA* as greater than the 90th percentile for gestational age based on sex-specific intrauterine growth curves (Olsen, Groveman, Lawson, & Clark, 2010).

Our primary outcome measure was the proportion of newborns at risk for NH who were exclusively breastfed at discharge, that is, newborns who exclusively received their own mother's breast milk by directly breastfeeding or by receiving expressed breast milk with no formula exposure during their hospital stays. Donor breast milk was not available for newborns who were not in the NICU during the 1-year period of our study. Secondary outcomes included the proportion of newborns at risk for NH who were admitted to the NICU for NH or needed IV dextrose bolus in the mother–baby unit and any occurrence of adverse effects of NH, such as seizures or coma.

Table 1: Comparison of Pre- and Post–Dextrose Gel Implementation Groups

	Before Implementation (n = 198)		After Implementation (n = 203)		
Variable	*M*	*SD*	*M*	*SD*	*p*
Maternal age, years	30.4	5.2	30.3	5.6	.85
Newborn gestational age, weeks	38.4	1.5	38.6	1.4	.25
Birth weight, g	3,326.8	709.7	3,380.4	709.4	.45
	Median	Range	Median	Range	
1-minute Apgar score	8	1–9	8	1–9	.21
5-minute Apgar score	9	6–9	9	7–10	.28
	n	%	*n*	%	
Male sex	91	45.9	102	50.2	.42
Late preterm	40	20.2	36	17.7	.61
Small for gestational age	30	15.2	39	19.2	.35
Large for gestational age	54	27.4	54	26.6	.91
Maternal race					.17
White	149	24.7	162	20.2	
Non-White	49	75.3	41	79.8	
Hypertensive disorders of pregnancy	20	10.1	26	12.8	.44
Chorioamnionitis	4	2.0	4	1.9	.99
ROM > 18 hours	5	2.5	2	0.9	.28
Mode of birth					.28
Vaginal	93	46.9	107	52.7	
Cesarean	105	53.0	95	46.8	
Multiple gestation	20	10.2	10	4.9	.06
Maternal diabetes	84	42.4	85	42.3	.99
Gestational	78	92.9	80	94.1	
Type 1	3	3.6	3	3.5	
Type 2	2	2.4	2	2.4	
Insulin	12	14.2	10	11.8	.66
Other medications	14	16.7	11	12.9	.52

Note. *M* = mean; ROM = rupture of membranes; *SD* = standard deviation.

To determine the differences in rates of exclusive breastfeeding and NICU admission before and after the intervention, we compared maternal and newborn characteristics and neonatal outcomes between the two cohorts. We used two-tailed Student *t* tests to analyze all continuous variables and Pearson chi-square tests of significance for all categoric variables. We determined statistical significance by using a $p < .05$ probability value. For all cell sizes less than 5 (e.g., NICU admissions), we used the Fisher exact *p* value for significance. We used SPSS (Version 25) for the analyses. We used Excel line graphs to provide a visual representation of exclusive breastfeeding rates at discharge before and after the intervention.

Table 2: Process and Outcome Measures

	Before Implementation (n = 198)		After Implementation (n = 203)		
Variable	n	%	n	%	p
Blood glucose > 50 mg/dL at 24 hours	132	67.3	143	70.4	.27
Dextrose gel	0	0.0	50	24.6	<.01
Intravenous dextrose bolus in mother–baby unit	1	0.5	1	0.5	.99
Exclusive breastfeeding at discharge	112	56.6	120	59.1	.62
NICU admission	5	2.5	3	1.5	.50

Results

The total numbers of neonates born in the hospital before and after the intervention were 972 and 986, respectively. During the preintervention period, 198 (20.4%) of 972 newborns were at risk for NH compared with 203 (20.6%) of 986 during the postintervention period. These newborns were otherwise clinically well and were admitted to the mother–baby unit. A comparison of maternal and newborn characteristics of the two groups is shown in Table 1. We found no significant differences in maternal and newborn characteristics between groups. The proportion of newborns of diabetic mothers and those who were SGA, LGA, and late preterm were similar.

Process and outcome measures are presented in Table 2. In accordance with the protocol, dextrose gel was given to 50 of 203 newborns (24.6%) in the postintervention group. NICU admissions for hypoglycemia remained infrequent during both time periods (2.5% of 198 vs. 1.5% of 203, $p = .50$). We found no significant difference in the proportion of newborns who were exclusively breastfed at discharge before and after the intervention (56.6% of 198 vs. 59.1% of 203, $p = .62$). We found no significant differences in the proportion of newborns with 24-hour blood glucose values greater than 50 mg/dL before and after the intervention (67.3% of 198 vs. 70.4% of 203, $p = 0.27$). In both groups, 0.5% of at-risk newborns received

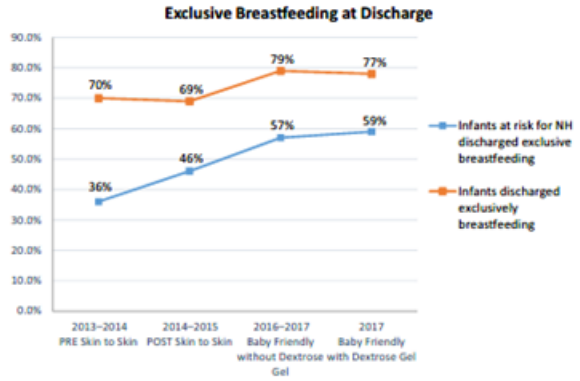


Figure 2. Line graph depicting the exclusive breastfeeding rates at discharge before the introduction of prolonged skin-to-skin care (2013–2014), after the introduction of prolonged skin-to-skin care (2014–2015), after the introduction of Baby-Friendly processes (2016–2017), and after the introduction of dextrose gel (2017). The blue line shows newborns at risk for neonatal hypoglycemia, and red line shows all the newborns in the mother–baby unit. NH = neonatal hypoglycemia.

For newborns at risk for NH, dextrose gel may not improve breastfeeding outcomes in a Baby-Friendly hospital.

a dextrose IV bolus in the mother–baby unit. There were no cases of seizures or coma in either group. The rates of exclusive breastfeeding at discharge before and after skin-to-skin care from our previous study are depicted in Figure 2 (Chiruvolu et al., 2017) and before and after dextrose gel from the current study.

Discussion

The management of NH remains challenging. Traditional treatment options, such as formula supplementation and IV dextrose, are not benign and may have long-term implications. Admission to the NICU results in separation of the newborn and mother, which may interrupt breastfeeding and bonding (Rawat et al., 2016). Multiple researchers have reported that after dextrose gel was introduced into the NH protocol, exclusive breastfeeding at discharge increased and admissions to the NICU decreased, although the breastfeeding data were less compelling than the NICU admission rates (Bennett et al., 2016; Makker et al., 2018; Rawat et al., 2016; Ter et al., 2017). Even though our Baby-Friendly hospital already had greater exclusive breastfeeding at discharge rates and lower NICU admission rates for NH compared with the facilities in many published studies, we opted to introduce dextrose gel into our NH protocol with the goal of further improving rates of exclusive breastfeeding at discharge.

Before the implementation of dextrose gel, we observed a gradual increase in rates of exclusive breastfeeding at discharge as we introduced prolonged skin-to-skin care and other Baby-Friendly processes (36.4% of 272 before skin-to-skin care vs. 45.7% of 289 after skin-to-skin care vs. 56.6% of 198 with Baby-Friendly processes before the introduction of dextrose gel; see Figure 2). After implementation of dextrose gel into the NH protocol, the proportion of newborns at risk for NH who were discharged exclusively breastfeeding was similar (59.1% of 203 vs. 56.6% of 198), as was the NICU admission rate (1.5% of 203 vs. 2.5% of 198). The introduction of dextrose gel did not have a significant further effect on outcomes for newborns at risk for NH. Our null findings may indicate that with Baby-Friendly processes in place, additional interventions such as dextrose gel may not further improve outcomes for newborns at risk for NH.

Skin-to-skin contact, hand expression of colostrum, early initiation of breastfeeding, and education of staff and parents are part of the evidence-based Ten Steps to Successful Breastfeeding, which are known to support optimal newborn feeding and bonding (World Health Organization, 2019). Baby-Friendly principles are physiologic processes that promote normal metabolic adaptation of newborns. Not only have these processes helped our hospital significantly decrease NICU admissions for NH, they also helped us to improve our rates of exclusive breastfeeding at discharge for all newborns.

Newborns in Baby-Friendly hospitals are more likely to be exclusively breastfed at discharge and are more likely to breastfeed longer (American Academy of Pediatrics, 2012). Successful establishment of breastfeeding is important because newborns who are suboptimally or not breastfed have an increased risk of short-term and long-term negative consequences, such as asthma, obesity, respiratory infections, eczema, sudden infant death syndrome, and lower intelligence scores (American Academy of Pediatrics, 2012; Victora et al., 2016). Critically, lactation intensity is one of the only modifiable factors to help prevent the development of Type 2 diabetes in women with a history of gestational diabetes (Gunderson et al., 2015). Because many newborns at risk for NH are born to women with diabetes, any treatment for NH should also consider the effect of the treatment on the establishment of breastfeeding for the health of the newborn and mother.

There are no known long-term benefits to the use of dextrose gel. Even though dextrose gel is believed to be safe for newborns, it is still a commercial product with flavorings and other additives. Harris et al. (2016) reported that toddlers who received dextrose gel as newborns had no differences in neurodevelopmental outcomes at 2 years compared with those who received placebo, but they did not study other potential effects. Although research results do not show risks of oral dextrose gel, the theoretical potential exists that its introduction could, like formula, alter the neonate's gut microbiome or metabolism. Further studies are needed to determine other long-term effects of dextrose gel, and researchers may take inspiration from studies of the risks of the introduction of complementary foods before age 6 months (Grimshaw et al., 2013).

Implications

For hospitals working to increase exclusive breastfeeding rates in newborns at risk for NH, implementation of core Baby-Friendly principles may be effective and yield long-term benefits for mothers and newborns. More studies are needed to determine the effects of dextrose gel on glycemic control, not just rates of exclusive breastfeeding and NICU admissions. Manufacturers should develop a standardized dextrose gel product for newborns, and studies should follow whether these standardized dosages would lead to better outcomes in newborns at risk for NH. Studies are also needed to examine the long-term effects of dextrose gel on newborns. Finally, research is needed to discover other interventions that specifically address breastfeeding support in newborns at risk for NH.

Limitations

This quasi-experimental pre- and postintervention study has several limitations. It was a single-center study to retrospectively compare two cohorts. It is possible that we did not observe any significant differences in outcomes because we had greater baseline rates of exclusive breastfeeding at discharge and low rates of NICU admissions. We may have approached a ceiling of improvement that can be made with hospital-based interventions alone. However, because of the paucity of data from Baby-Friendly hospitals in the United States and many other hospitals pursuing Baby-Friendly designation, we believed it was important to report our observations. Another limitation is that we were unable to perform a randomized controlled trial because the random assignment of mothers and newborns away from evidence-based practices, such as skin-to-skin care, is not ethical. As such, because our study was not a randomized experimental design, confounding potentially limited our findings. Our analyses were bivariate, without adjustment for potential confounders such as maternal education level and body mass. However, we believe that these initial findings are substantive and should lead to more complex study designs in the future.

The concentration of glucose can vary among different brands of dextrose gel and within the same tube (Solimano, Kwan, Osiovich, Dyer, & Elango, 2018). This could potentially affect our findings in that we were unable to standardize concentration levels that newborns received from one tube; we did, however, use a single brand. Last, external validity of our findings was limited because of the nature of the population served in our suburban setting. We plan to study this topic in one of our larger, more urban facilities in the future.

Conclusion

We successfully implemented dextrose gel into the NH protocol of a community Baby-Friendly hospital. Of the 203 newborns at risk for NH, 25% qualified for administration of the gel. We observed that gel introduction had no significant effects on the rate of exclusive breastfeeding at discharge or NICU admissions in newborns at risk for NH beyond what we had previously achieved by introduction of prolonged skin-to-skin and other Baby-Friendly processes.

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Glucose Gel as a Treatment for Neonatal Hypoglycemia

CHAPTER 3

HOW MUCH GLUCOSE IS IN THE GEL USED TO TREAT NEONATAL HYPLOGLYCEMIA?

HOW MUCH GLUCOSE IS IN THE GEL USED TO TREAT NEONATAL HYPOGLYCEMIA?

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Funding information
This study was funded by a grant received from the University of Texas at Arlington Center for Research and Scholarship. Additional funding was provided by the University of Texas at Arlington Bone-Muscle Research Center.

Abstract

Objective To measure glucose concentration within and among tubes of the oral glucose gels most commonly used to treat neonatal hypoglycemia (NH) in the United States, Glutose 15™ and Insta-Glucose™.

Study Design A laboratory study measuring and comparing glucose content in aliquots taken from the top, middle, and bottom sections of 3 different lots and in whole tubes from 3 different lots.

Results The percent difference observed between the 3 sections of Glutose 15™ tubes was 12.3-53.8% and between the 3 sections of Insta-Glucose™ tubes was 40.7- 79.6%. The difference in concentration of glucose between 3 lots of whole tubes of Glutose 15™ was 1.6% and between 3 lots of whole tubes of Insta-Glucose™ was 8.8%.

Conclusion Glucose is not uniformly distributed within tubes of Glutose 15™ and Insta-Glucose™ and this may account for variable results on the efficacy of oral glucose gel as a treatment for NH.

Introduction

One of the primary physiological challenges that newborns experience during the transition to extrauterine life is the maintenance of blood glucose [1]. Neonatal hypoglycemia (NH) is a blood glucose level low enough that delivery to critical organs may be compromised [2]. Prolonged and severe episodes of NH are associated with neurological injury and treatment of NH in the United States costs about $2.1 billion each year [3-4].

Approximately 30% of otherwise healthy newborns have risk factors for NH at birth and require blood glucose screening [5]. About half of those screened will experience at least one episode of NH requiring intervention [6]. Newborns admitted to a mother baby unit are considered at risk for NH if they are born late preterm (between 34-37 weeks of gestation), small for gestational age (SGA) (at a birth weight less than the 10th percentile), large for gestational age (LGA) (at a birth weight greater than the 90th percentile), or if their mothers are diabetic [7].

The most common treatment for NH is formula feeding. However, formula feeding is associated with early cow's milk protein exposure and reduced insulin sensitivity, predisposing infants to Type 1 and Type 2 diabetes [8]. In addition, it may interfere with the establishment and duration of breastfeeding and may increase the neonate's risk of infection and allergies by changing the natural gut microbiome [9]. If treatment with formula feeding is unsuccessful in stabilizing blood glucose values, newborns are often transferred to the neonatal intensive care unit (NICU) for intravenous dextrose infusions. However, this results in the separation of the newborn and the mother, which may interrupt breastfeeding and bonding and lead to long-term adverse effects [4].

A relatively new treatment for NH is oral 40% glucose gel. The Sugar Babies study, a randomized, double-blinded, placebo-controlled trial from New Zealand, found that administering oral 40% glucose gel was more effective in maintaining adequate blood glucose

control than a placebo [6]. They also found that infants who were given glucose gel were less likely than infants given placebo gel to be admitted to the NICU for NH and received significantly less expressed breastmilk and fewer formula feedings. After the publication of this study, multiple research groups around the world introduced oral 40% glucose gel in the treatment protocols for NH and published their observations. Several reported a wide range of decreased NICU admission rates for NH from 2-73% [4, 5, 10, 11, 12]. In contrast, a few other groups, including our team in a previous report, found no significant difference in NICU admission rates before and after the introduction of glucose gel [13-15]. Similarly, several groups reported that the implementation of glucose gel was associated with an increase in the exclusive breastfeeding rate at hospital discharge by 9- 49%, but two other groups reported no significant change in the exclusive breastfeeding on discharge rate after implementation of glucose gel [4, 5, 10, 13, 14, 15].

One reason for the mixed results of the efficacy of oral glucose gel could be due to the inconsistency in the dosage of glucose found in commercially available oral glucose gel. In the Sugar Babies study, the glucose gel was compounded in the hospital's pharmacy. Many of the subsequent researchers used commercially available oral glucose gels that were originally intended for adult diabetics experiencing hypoglycemia. A research group from Canada reported that the glucose content in a tube of commercially available glucose gel can vary by as much as 81% between batches and in doses tested from different areas of the tube [16]. Therefore, a newborn given the same volume of glucose gel from the first section of the tube may not receive the same dose of glucose as a newborn receiving gel from the end of the tube. There are no published studies on consistency of glucose gel in the commercial brand most commonly used in the United States.

The purpose of this study is to measure glucose concentration within and among tubes of the two most-commonly used commercial oral glucose gels in the United States, Glutose 15™ (Perrigo, Minneapolis, MN) and Insta-Glucose™ (Valeant Pharmaceuticals North America LLC, Bridgewater, NJ).

Material and Methods

The glucose content in oral glucose gel was measured by using hexokinase and glucose-6-phosphate dehydrogenase enzymes on the Siemens ADVIA 1800 analyzer (Siemens Healthcare Diagnostics, Inc., Tarrytown, NY). Since this analyzer is typically used to measure glucose in serum, laboratory personnel first performed a series of standard laboratory validation studies on Glutose 15™ Lot #0120988 and Insta-Glucose™ Lot #8125416 during which they validated that the analyzer measured glucose accurately and precisely in the glucose gel substrate [17, 18] (see Supplementary Material for further details).

To determine if there were differences in glucose concentrations in aliquots taken from different areas of the tubes of gel, we used tubes from three distinct lots of Glutose 15™ (#9510096, #9499927, and #120988) and Insta-Glucose™ (#200315, #8116975, and #811697). Since the gel was too viscous to pipette accurately, the glucose gel tubes were carefully sliced using a surgical knife into top, middle, and bottom sections of approximately equal lengths. A minimum of 0.1000 g of glucose gel was weighed from each section using a Mettler Toledo XS204 analytical balance (Columbus, OH). The gel was then dissolved in a minimum of 10 mL deionized water and diluted, if necessary, to achieve a glucose concentration within the analytical measurement range (AMR). Glucose was measured in 20 replicates. An average concentration was normalized per gram of glucose gel and a comparison was performed between the top, middle, and bottom sections.

To determine if glucose concentrations differed among lots of oral glucose gel tubes, the contents of the whole tube were dissolved in one liter of deionized water. They were then diluted further to achieve a glucose concentration within the AMR. Next, the glucose concentration was measured in 5 replicates for each of the 3 lots of Glutose 15™ and Insta-Glucose™ and a comparison was performed between the lots. An average concentration was normalized per gram of glucose gel and a comparison was performed between the lots.

Results

The lowest % difference observed between any of the 3 sections of a Glutose 15™ gel tube was 12.36%, and the highest difference was 53.77%, indicating that glucose was not uniformly distributed in the gel tube (Table 1).

Table 1. Glucose concentration in three sections of Glutose 15™ gel

	% Glucose in Gel				
Lot #	**Top**	**Middle**	**Bottom**	**Difference (H - L)**	**% Difference (H vs L)**
9510096	49.02 ± 0.11	46.15 ± 0.15	70.96 ± 0.19	24.81	53.77
9499927	48.26 ± 0.10	40.92 ± 0.17	40.63 ± 0.15	7.63	18.78
120988	44.54 ± 0.13	42.56 ± 0.22	39.64 ± 0.21	4.90	12.36
H: Highest concentration, L: Lowest concentration					

The lowest % difference observed between any of the 3 sections of a Insta-Glucose™ gel tube was 40.73%, and the highest difference was 79.59%, indicating that glucose was not uniformly distributed in the gel tube (Table 2).

Table 2. Glucose concentration in three sections of Insta-Glucose™ gel

	% Glucose concentration in Gel				
Lot #	**Top**	**Middle**	**Bottom**	**Difference (H - L)**	**% Difference (H vs L)**
200315	22.27 ± 0.06	15.26 ± 0.04	18.63 ± 0.11	7.01	45.94
8116975	18.51 ± 0.04	15.30 ± 0.12	27.47 ± 0.09	12.17	79.59
8116977	21.22 ± 0.04	23.15 ± 0.05	16.45 ± 0.05	6.70	40.73
H: Highest concentration, L: Lowest concentration					

The difference in concentration of glucose between 3 lots of Glutose 15™ was 1.6% (Table 3). The difference in concentration of glucose between 3 lots of Insta-Glucose™ was 8.8% (Table 3).

Table 3. Glucose concentration in various lots of glucose gels

Glutose 15™ Lot #	9510096	9499927	120988	Difference: H - L	% Difference vs L
Glucose (%)	49.1	48.4	48.3	0.8	1.6
Insta-Glucose™ Lot #	200315	8116975	8116977		
Glucose (%)	18.8	17.2	17.6	1.5	8.8

H: Highest concentration L: Lowest concentration

Discussion

The use of oral 40% glucose gel as a treatment for NH is increasing and being integrated into guidelines by expert societies [19, 20]. We found acceptable differences in glucose concentration between the lots; however, discrepancies were noted in the glucose concentration within the tubes of Glutose 15™ and Insta-Glucose™, the two most commonly-used oral glucose gels in the United States. These inconsistencies could influence the effectiveness of this intervention.

In the Sugar Babies study, researchers used an oral glucose gel formulation that was compounded in the hospital pharmacy for the trial. After the publication of this study, other hospitals around the world started using glucose gel, but in the absence of a product specifically made for newborns. Commercially available oral glucose gels meant for diabetes care in adults were incorporated into NH protocols. An adult would take an entire tube as a dose, but for newborns approximately 11 doses are extracted from a single tube (Trickey, S.P., November 19, 2019). Therefore, consistency of glucose in aliquots extracted from the different parts of the same tube calls into question the validity and generalizability of reported outcomes. Because

these products are over-the-counter and not regulated, the manufacturers are not required to do consistency studies (Smith, K.J, personal communication, November 3, 2019).

There are other drawbacks to using oral glucose gels intended for adult diabetes care to treat newborns for NH. They contain flavorings and preservatives that have an unknown effect on a newborn's developing microbiome. Additionally, the viscosity of the gel makes it challenging to withdraw precise volumes of the tube into oral syringes for administration and this could lead to newborns receiving variable doses of glucose other than intended 0.5 ml/kg of glucose gel. Finally, though researchers from the Sugar Babies study concluded there were no long-term adverse effects with oral glucose gel, we cannot conclude the same safety for other commercially available glucose gels [21]. The long-term effects of the flavorings, preservatives, and variable concentration of glucose are not known.

Our study builds on the work of Solimano et al., who tested Insta-Glucose™ and Dex4™, the most commonly-used oral glucose gels in Canada [16]. We tested the two most commonly-used oral glucose gels in the United States, Glutose 15™ and Insta-Glucose™. Similar to their results, we found marked variation in the concentration of glucose from top, middle, and bottom parts of the tube. These results are concerning as the impact on newborns receiving doses other than 0.2 grams/kg (40% oral glucose gel 0.5 mL/kg) of glucose bolus are not known. Slow or rapid recovery from hypoglycemia is reported to be associated with long-term neurosensory impairment [22]. We noted acceptable variation in concentrations of glucose when we examined the content of entire tubes from different lots.

A key limitation of this study is this was a laboratory study and the actual methods that hospital pharmacists use to collect individual glucose gel doses may vary. While at many hospitals the gel is drawn directly from the tube into syringes, some express all of the gel into a

different container before drawing it into syringes. These different methods could produce different results than this laboratory study. An additional limitation is that the laboratory only tested for glucose. Other carbohydrates present in the gel may also vary and have some clinical significance.

Recommendations for future research involve the development of a quality-controlled oral glucose gel that is custom-made for newborns with limited flavorings and additives. This product should come in pre-filled oral syringes in doses typically used for newborns. This would aid in the administration of correct doses of gel. Future studies should be conducted to determine whether the use of these standardized products would lead to glycemic control for newborns with NH. Additionally, studies should be conducted on the long-term outcomes of newborns who are treated with the adult diabetes care oral glucose gels and on the effects of these products on the newborn microbiome. Finally, research is needed to discover other interventions that could improve outcomes for newborns with NH while preserving breastfeeding and mother-baby bonding.

Conclusion

To conclude, we tested Glutose 15™ and Insta-Glucose™, the two oral glucose gels most commonly used for the treatment of NH in the United States and found that glucose is not uniformly distributed within tubes. The percent difference observed within a tube of Glutose 15™ tube was up to 53.8% and within a tube of Insta-Glucose™ tube was up to 79.6%. These inconsistencies mean that newborns may not be receiving the dose of glucose that their providers intended and this could account for the variable results in clinical outcomes for newborns treated for NH. Given that 15% of newborns are at risk for NH, there is a need for a quality-controlled,

single-dose, newborn-specific product that is free of flavoring and contains only preservatives known to be safe for newborns.

Acknowledgements
We would like to acknowledge Alice Gallegos, Technical Specialist in Chemistry, for her work in performing this series of lab tests.

Conflict of interest
The authors declare no conflict of interest or relevant financial relationships.

Author contributions
KS was responsible for the original conception of the study, securing the funding, conducting the literature review, creating the discussion section and the reference list, and writing the final report. VK was responsible for designing the laboratory study and writing the methods and results sections. AC provided feedback on the clinical implications of the findings. DC provided feedback on the report.

Funding information
This study was funded by a grant received from the University of Texas at Arlington Center for Research and Scholarship. Additional funding was provided by the University of Texas at Arlington Bone-Muscle Research Center.

Supplementary information is available at JPER's website.

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Supplementary Materials

Results of Validation Studies

Precision:

Serum from 20 patient samples were pooled and analyzed in duplicate to determine target concentration. Intra-assay precision was conducted by analyzing 20 replicates of glucose gel solutions prepared in deionized water, saline, and serum (pooled), at three concentrations (low, mid, high) spanning the analytical measurement range (AMR) of the method. Inter-assay precision was assessed by analyzing the above samples in duplicate over a period of at least 5 days.

Table 1. Intra-assay precision of Glucose in Gels

Glutose 15 in DI Water	**Low**	**Medium**	**High**	**Glutose 15 in Saline**	**Low**	**Medium**	**High**	**Glutose 15 in Pooled Serum**	**Low**	**Medium**	**High**
Average	67.0	341.4	672.9	Average	69.0	342.7	677.6	Average	108.9	356.9	657.4
SD	0.0	1.8	2.4	SD	0.0	1.1	2.1	SD	0.7	1.8	2.2
%CV	0.0	0.5	0.4	%CV	0.0	0.3	0.3	%CV	0.7	0.5	0.3
Insta-Glucose in DI Water	**Low**	**Medium**	**High**	**Insta-Glucose in Saline**	**Low**	**Medium**	**High**	**Insta-Glucose in Pooled Serum**	**Low**	**Medium**	**High**
Average	59.0	293.1	582.6	Average	57.6	284.5	559.6	Average	101.6	305.4	556.0
SD	0.0	1.1	2.4	SD	0.5	0.8	1.2	SD	0.6	1.0	2.5

%CV	0.0	0.4	0.4	%CV	0.9	0.3	0.2	%CV	0.6	0.3	0.5

Table 2. Inter-assay Precision of Glucose in Gels

Glutose 15	**Average**	**Standard Deviation**	**%CV**
Low	143.6	0.73	0.51
Medium	228.1	1.05	0.46
High	502.2	3.73	0.74
Insta-Glucose	**Average**	**Standard Deviation**	**%CV**
Low	183	0.71	0.39
Medium	352.9	1.45	0.41
High	525.7	1.73	0.33

Clinical Laboratory Improvement Amendments (CLIA) proficiency testing criteria for acceptable analytical performance for glucose (serum) is +/- 10% or +/- 6 mg/dL that we term as Total Allowable Error, i.e., TEA [1]. Coefficient of variation (%CV) of TEA/3 is considered acceptable for glucose measurement. Intra-assay and Inter-assay precision for glucose measurement in all matrices was excellent as it never exceeded TEA/10.

Accuracy/Recovery:

The contents of one whole tube of Glutose 15 gel™ were dissolved in 1 liter of deionized water, and then diluted 4 in 10 to obtain the concentration with the analytical measurement range

(AMR) of the method. The target glucose concentration of pooled serum was 87.5 mg/dL, and that of Glutose 15™ 730.9 mg/dL. The calculated concentration of glucose from the whole tube was 1791 mg/dL (17.91 g/tube), which was higher than listed on the package (15 grams).

The contents of one whole tube of Insta-Glucose™ was diluted in 1 liter of deionized water and then diluted 1 in 4 to achieve concentration within AMR. The calculated concentration of glucose from the whole tube was 540 mg/dL (5.4 g/tube). Since Insta-Glucose contains dextrose, dextrins, and maltose, and this method can only measure glucose (dextrose), our results suggest that glucose makes only a fraction of total of 24 grams of sugars.

To assess recovery of glucose from gel, we analyzed the admixtures of pooled serum and glucose gel prepared as shown in Table 3 and 4.

Table 3. Recovery of Glutose 15™ in Serum Matrix

Specimen	Target	Rep 1	Rep 2	Average	% Recovery
Serum 100%	87.5	87.6	87.3	87.5	100.0%
G:S (25% : 75%)	248.3	256.3	254.8	255.6	102.9%
G:S (50% : 50%)	409.2	420.1	420.3	420.2	102.7%
G:S (75% : 25%)	570.0	573.1	575.1	574.1	100.7%
Glutose 15 100%	730.9	731.0	730.7	730.9	100.0%

Table 4. Recovery of Insta-Glucose™ in Serum Matrix

Specimen	Target	Rep 1	Rep 2	Average	% Recovery

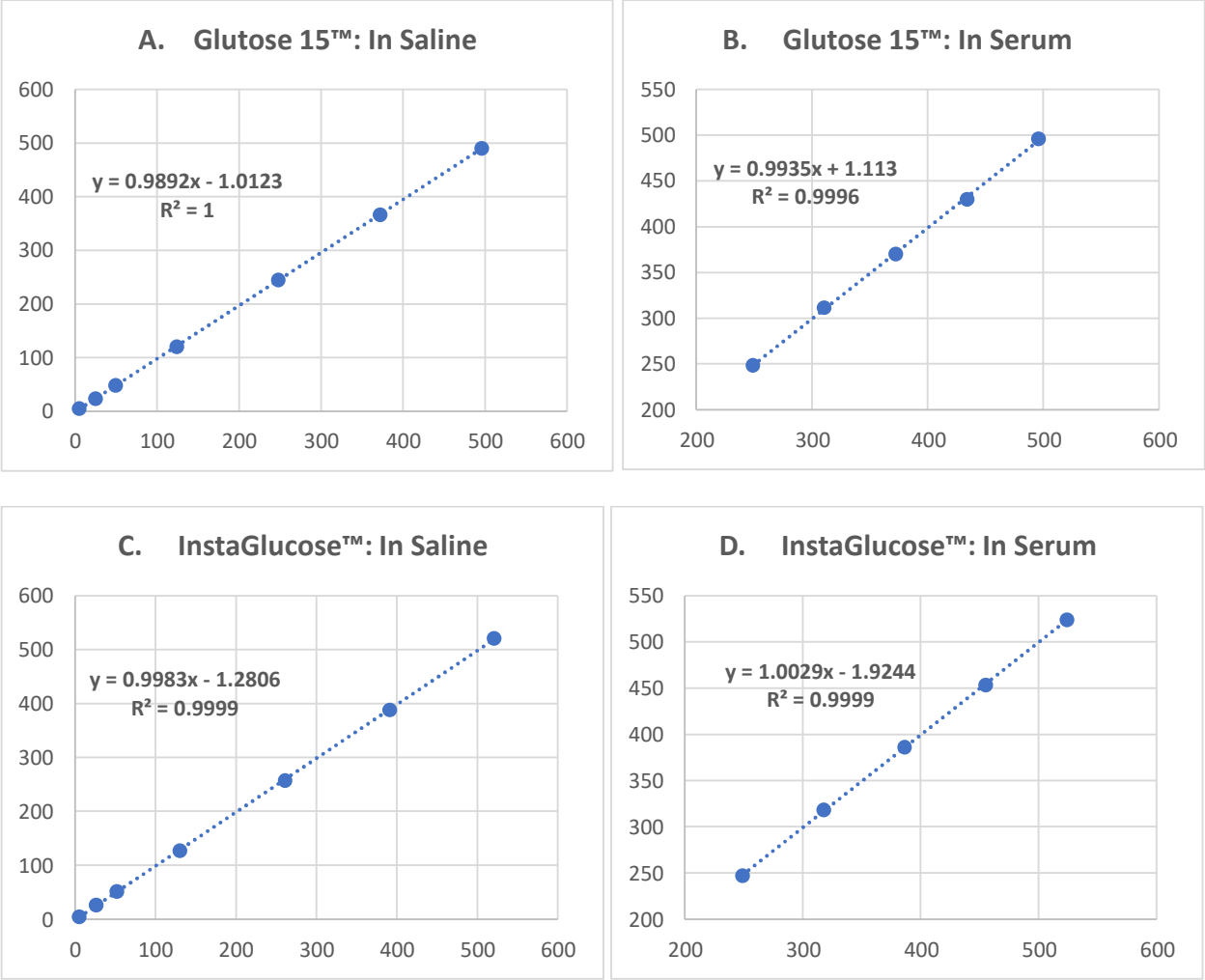
Serum 100%	**88.0**	**88.1**	**87.9**	**88.0**	**100.0%**
IG:S (25% : 75%)	**103.0**	**104.9**	**104.1**	**104.5**	**101.4%**
IG:S (50% : 50%)	**118.1**	**119.6**	**118.8**	**119.2**	**100.9%**
IG:S (75% : 25%)	**133.2**	**132.7**	**133.6**	**133.2**	**100.0%**
IG 100%	**148.3**	**148.3**	**148.2**	**148.3**	**100.0%**

Recovery of glucose in serum matrix for both Glutose 15™ and Insta-Glucose™ at all three levels was excellent and within 3% of expected concentration. These results demonstrate that ADVIA 1800 glucose measurement method can be used to conduct subsequent experiments to assess if glucose concentration was uniform in the gel tubes.

Analytical Measurement Range (AMR)/Linearity:

A mixture of glucose gel with either saline or pooled serum was prepared to obtain 5 to 7 glucose concentrations spanning the AMR. Expected values based upon duplicate analysis of glucose gel solutions and pooled serum were then plotted against the observed average of duplicate values. Glucose measurement in both Glutose 15™ and Insta-Glucose™ exhibited excellent linearity over the analytical measurement range as shown in Figures 1A – 1D. Glucose in Glutose 15™ and Insta-Glucose™ diluted in saline showed slopes of 0.9892 and 0.9983, and R2 values of 1.0 and 0.9999, respectively. Glucose in Glutose 15™ and Insta-Glucose™ diluted in pooled serum showed slopes of 0.9935 and 1.0029, and R2 values of 0.9996 and 0.9999, respectively.

Figure 1. Linearity of Glucose in Saline and Serum matrices



Limit of Quantification (LOQ):

Blank and sample at the lowest concentration (2.0 mg/dL, vendor suggested LOQ) were analyzed at least 10 times and the distribution observed to not overlap, thereby verifying that 2.0 mg/dL as the LOQ for this method.

Stability:

Aliquots of both glucose gels at low, mid, and high glucose concentrations analyzed on days 0, 2, 3, 4 and 6 days showed the difference was 0.65%, 0.77%, 0.37% and 0.33% respectively. These aliquots were stored in a refrigerator over the days of study. Since the % difference was well

below TEA (10%), these data suggest that upon dilution glucose is stable for at least 6 days when stored refrigerated.

Reference:

1. Federal Register February 28, 1992;57(40):7002-186.

Glucose Gel as a Treatment for Neonatal Hypoglycemia

CHAPTER 4

CONCLUSIONS

Treatment for NH remains challenging. Traditional treatments like formula supplementation for breastfeeding newborns and transfer of neonates to the NICU for intravenous dextrose infusions may be effective, but they are not benign interventions and may have lasting negative outcomes. Oral dextrose gel is a relatively new treatment for NH. Clinicians and researchers hoped that its use would adequately stabilize blood glucose in newborns experiencing NH, while also avoiding the negative consequences of interrupting exclusive breastfeeding and parent-child separation.

In this dissertation, the author presents two manuscripts that add to the body of knowledge about oral glucose gel when used as a treatment for NH. In the first manuscript, the gap in the literature about the effectiveness of oral dextrose gel as a treatment for NH in a Baby-Friendly hospital with a high baseline exclusive breastfeeding rate and a low baseline NICU admission rate was addressed. The findings show no significant increase in exclusive breastfeeding rates at hospital discharge or any significant decrease in NICU admission rates for NH after the introduction of the gel.

After completion of the first study, the author learned of a Canadian study that showed a significant variation in the glucose concentration in aliquots extracted from different areas of a glucose gel tube or different lots of glucose gel (Solimano et al., 2018). This was identified as a gap in the literature because no similar studies had been performed on the brands used in the United States. This led the author to obtain grant funding to test the two most commonly used oral glucose gels in the United States for their consistency. Laboratory studies found that glucose

was not uniformly distributed within tubes of Glutose 15™ and Insta-Glucose™ and this may account for mixed results on the efficacy of oral glucose gel as a treatment for NH.

Limitations of Manuscript One

The study reported in Manuscript One was a pre-and post-intervention study and has several limitations. First, the data was collected retrospectively from chart reviews. As such, the authors could not verify data accuracy. Data collection could be better controlled in the future by performing prospective studies. An additional limitation is that this study was conducted at a single site in a suburban setting. This limits the external validity of the findings. There may have been no observed significant differences in outcomes because the study site already had high baseline rates of exclusive breastfeeding and low NICU admission rates. As such, the hospital may have already reached a ceiling of improvement that can be achieved with hospital interventions alone. Finally, the concentration of glucose in over-the-counter glucose gel may vary among different brands and tubes of gel. This could have confounded the results of this study.

Limitations of Manuscript Two

Concern about the consistency of dosing from over-the-counter oral glucose gels used to treat NH led the authors to conduct the study reported in Manuscript Two. This study was a laboratory study and the actual methods pharmacists at hospitals use to collect individual glucose gel doses may vary. While the pharmacists at some hospitals draw the gel directly from the tube into syringes, others express all the gel into a different container before drawing it into syringes. These different methods could produce different results than this laboratory study. An additional limitation is that the laboratory is only testing for glucose. Other carbohydrates could be present in the gel and this could have some clinical significance.

Implications for Nursing Practice

Manuscript One

Though a safety study of glucose gel found no neurological differences between two-year-old children who had been treated as neonates for NH with glucose gel and those who had been given a placebo, the gel is a commercial product that contains additives and flavorings that have the potential to alter the neonatal gut microbiome or metabolism (Harris et al., 2016). Baby-Friendly principles like staff education, parent education, skin-to-skin contact between parent and newborn, hand expression, and early breastfeeding initiation are physiologic processes that promote metabolic adaptation and yield long-term benefits to mothers and newborns. For clinicians and leaders working in hospitals that are following these physiologic processes well, the addition of glucose gel might not make any further impact.

Manuscript Two

In the benchmark Sugar Babies study, researchers used a glucose gel formulation that was compounded for the trial. After the release of their results, other sites around the world started using glucose gel, but in the absence of a commercially available product meant for newborns, they used commercially available glucose gels meant for diabetes care in adults. However, the authors of this manuscript found discrepancies in the formulations of Glutose 15™ and Insta-Glucose™, the two most used oral glucose gels in the United States. These inconsistencies could affect the action of this intervention.

There are other drawbacks to using adult diabetes care glucose gels to treat newborns for NH. They contain flavorings and preservatives that have an unknown effect on a newborn's developing microbiome. Additionally, the viscosity of the gel makes it challenging to withdraw precise volumes of the tube into oral syringes for administration and this could lead to newborns

receiving variable doses of glucose. Finally, though researchers followed the neonates from the Sugar Babies study for their first two years of life and found that the gel was safe, this safety study was done on newborns receiving the pharmacy-compounded gel, not the commercially available adult diabetes care products that other sites are using (Harris et al., 2016). Therefore, the long-term safety of these products when used for neonates is unknown.

Future Research

Manufacturers should develop a quality-controlled oral glucose gel that is specifically made for newborns with limited flavorings and additives. This product should come in pre-filled oral syringes in doses typically used for newborns. This would aid in the administration of correct doses of gel. Then, studies should follow to determine whether the use of these standardized products would lead to better outcomes for newborns with NH. Additionally, studies should be conducted on the long-term outcomes of newborns who are treated with the adult diabetes care oral glucose gels and on the effects of these products on the newborn microbiome. Finally, research is needed to discover other interventions that could improve outcomes for newborns with NH while preserving breastfeeding and parental-child attachment.

Research is also needed to discover other interventions that specifically address breastfeeding support in neonates at risk for NH. Prospective studies on antenatal hand expression for mothers who are at risk for having a baby with NH, prolonged skin-to-skin contact between mothers and newborns at risk for NH, and the use of pasteurized donor breastmilk in newborns experiencing NH are areas that should be explored.

Researchers should report the brand of gel they used in their studies. The authors of Manuscript Two had to contact the authors of about half the published studies to inquire as to the brand they used in their studies. Research on NH has primarily focused on the effects of

treatments like breastfeeding, formula feeding, intravenous infusions, and oral dextrose gel (Harris et al., 2013). Though there are studies on how social determinants of health like race and access to healthy food affect risk factors for NH like preterm birth and maternal diabetes, there are no studies on the direct effects of these social determinants on NH. Research in this area could help prevent, not just treat, NH. Researchers could help by reporting the racial and ethnic demographics not just of their sample, but of the entire population of neonates born at their hospitals. This will allow readers to determine if NH disproportionately affects newborns from certain communities.

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Appendix A

IRB Letter

UNIVERSITY OF TEXAS ARLINGTON | OFFICE OF RESEARCH ADMINISTRATION
REGULATORY SERVICES

December 19, 2019

Karen Stanzo
Nursing
The University of Texas at Arlington

IRB Submission Inquiry & Project Determination of Non-HSR

Good afternoon Karen Stanzo,

Thank you for contacting the UT Arlington Office of Research Administration; Regulatory Services regarding a study to be conducted that will analyze glucose concentrations in two commonly used in over-the-counter oral glucose gels, Glutose 15 and Insta-Glucose.

Upon reviewing the procedures involved with the study, it appears they would not meet the definition of, "research with human subjects" as defined by the Office for Human Research Protections (OHRP) and would therefore not be subject to review or approval by the Institutional Review Board (IRB) at UT Arlington. Per the federal regulations at 45 CFR 46:

- *Research* is defined as, "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."
- A *human subject* in research is defined as, "a living individual about whom an investigator conducting research: obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens."

From the description of procedures provided, it appears that this study does not meet the definition of human subject research, as the protocol does not involve human subjects.

Therefore, this project is not subject to review or approval from the UTA IRB, and you do not need to submit a protocol to our office at this time.

It is your responsibility to abide by the UT Arlington Standards of Conduct and the ethical standards within your field for all projects and activities, even when IRB review is not required.

I have included the link for decision charts provided from OHRP from which this determination is made for your reference below. If the procedures that have been outlined and provided to our office change such that IRB approval might be necessary or you have any questions regarding this determination, please do not hesitate to contact us at RegulatoryServices@uta.edu .

Thank you,

Christina Morris
IRB Specialist

REGULATORY SERVICES
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Appendix B

Manuscript Submission Letter -The Journal of Perinatology

Stanzo, Karen C

From: jperinatol@us.nature.com
Sent: Wednesday, June 30, 2021 9:59 AM
To: Stanzo, Karen C
Subject: {EXTERNAL} 21-677 Receipt of Manuscript by the Journal of Perinatology

30th Jun 2021

Dear Ms. Stanzo:

Title: HOW MUCH GLUCOSE IS IN THE GEL USED TO TREAT NEONATAL HYPOGLYCEMIA?
Corresponding Author: Ms Stanzo

Your manuscript has been received and is currently being reviewed by the Editorial Board. You will be notified as soon as this process is completed.

Your manuscript has been allocated the number 21-677. Please refer to the manuscript number cited above when making inquiries.

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Sincerely,

Patrick Gallagher, M.D.
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