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ORIGINAL ARTICLE

Neonatal hypoglycemia: glucose gel efficacy in the treatment of early hypoglycemia in newborns with risk factors. Randomized clinical trial

Hipoglucemia neonatal: eficacia de la glucosa gel en el tratamiento de la hipoglucemia precoz en recién nacidos con factores de riesgo. Ensayo clínico aleatorizado

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What do we know about the subject matter of this study?

Neonatal hypoglycemia is a frequent metabolic disorder in newborns with risk factors. The administration of 40% glucose gel in the oral mucosa represents an effective treatment, with no adverse events described and at a low cost, avoiding undesirable mother-infant separations and favoring breastfeeding at discharge.

What does this study contribute to what is already known?

This randomized clinical study of equivalence between the administration of 40% glucose gel and infant formula, in the face of asymptomatic neonatal hypoglycemia in newborns with risk factors, shows less success with glucose gel than with formula, with no difference in the risk of hospitalization.

Abstract

Hypoglycemia is the most frequent metabolic disorder in newborns; the administration of 40% glucose gel in the oral mucosa could be as effective in its correction as the administration of formula milk, not interfering with breastfeeding. **Objective:** To evaluate the efficacy of 40% glucose gel compared with formula milk in the treatment of early asymptomatic hypoglycemia in newborns with risk factors. **Patients and Method:** Randomized clinical trial, non-inferiority, conducted in a private hospital. Newborns attended in rooming-in with the following risk factors were included: late preterm, large and small for gestational age at term, and children of diabetic mothers. In the presence of hypoglycemia, one group received 40% glucose gel (A) in the oral mucosa and another group received formula milk (B). Therapeutic failure was considered as persistence or repetition of hypoglycemia in the first 48h of life. **Results:** 866 NBs with risk factors were registered over 36 month; 278 (32.1 %) presented hypoglycemia; 105 NBs in group A and 115 in group B completed the study. 75 (71 %) NBs in group A and 104 (90,4 %) in group B achieved hypoglycemia correction. After analyzing the trends obtained, it was decided to discontinue the study. **Conclusions:** The administration of 40% glucose gel was not equivalent to the administration of formula milk in the treatment of early asymptomatic hypoglycemia in newborns with risk factors.

Keywords:
Newborn;
Neonatal Hypoglycemia;
Asymptomatic Hypoglycemia;
Risk Factors;
Glucose Gel

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Introduction

Neonatal hypoglycemia (NH) is detected in 10-15% of newborns (NB) and is a preventable cause of brain damage[1]. The fetus depends on the flow of glucose across the placenta to meet its metabolic demand. After birth, glucose levels drop sharply during the first 4 to 6 hours, with homeostasis depending on adequate glycogen storage and balance between glucose-regulating hormones (insulin-glucagon). This physiological process can be altered, mainly in children with risk factors.

There are discrepancies in normal glycemia values in newborns during the first hours of life. Marvin Cornblath, a pioneer in describing NH and its treatment, stated in 2000 that its definition remained controversial[2].

The American Academy of Pediatrics (AAP) establishes NH as < 25 mg/dL (1.4 mmol/L) in the first 4 h, < 35 mg/dL (2.0 mmol/L) between 5 and 24 h, and < 45 mg/dL (2.5 mmol/L) from the second day[3]. However, the Pediatric Endocrine Society establishes somewhat higher values[4].

In 2019, a review of standard practices in NH, published by the Fetal-Neonatal Studies Committee (CEFEN) of the Argentine Society of Pediatrics, defines NH with a blood glucose value < 47 mg/dl (2.6 mmol/L) from 24 h of life; adhering to the AAP definitions for the first day[5].

Essentially, all these recommendations establish a relationship with psychomotor development; they are observational data and expert opinion (low quality of evidence), concluding that blood glucose values should be maintained > 40 mg/dl in the first hours of life and > 45 mg/dl until 48 h. Two studies published in 1988 concluded that there would be no neurodevelopmental risk with blood glucose values > 47 mg/dl in the first days of life. Dani and Corsini question whether these values are currently acceptable[6-8].

Van Kempen et al. in the HypoEXIT Study Group described in late preterm and term newborns with risk factors for hypoglycemia, values of 36 mg/dL and 47 mg/dL in the first two days that were not associated with differences in psychomotor development at 18 months of life[9].

The classic treatment of asymptomatic NH with infant formula could interfere with breastfeeding, a biological process of great importance for the newborn both in the short- and long term. Since 1991, the "Baby-Friendly Hospital" initiative (WHO-UNICEF) has been promoting the implementation of practices that protect and support breastfeeding[10]. Perrine et al. emphasize that a determining factor in continuing exclusive breastfeeding is the support of breastfeeding from birth and reaffirming it during the hospital stay[11]. Also, Walker M. affirms that the incorporation of a single bottle with formula could alter the intestinal flora for 4 weeks[12].

Therefore, there is a need for a valid therapeutic option that resolves asymptomatic NH in term or near-term NBs, without the use of formula or hospitalization, which alters the mother-child relationship. In 2013, Harris et al. developed a promising therapy using 40% glucose gel to resolve hypoglycemia in asymptomatic neonates with risk factors since its administration on the oral mucosa with its developed vascularization would favor its rapid absorption. The authors describe it as a reliable, safe, effective, and low-cost treatment, with no reports of adverse effects in a follow-up at 2 years[13]. In a recent Cochrane review, the Liggins Institute of New Zealand chaired by Jane Harding, ratifies the usefulness, simple administration, and lack of risk of 40% glucose gel to correct asymptomatic hypoglycemia in newborns in the first days of life[14].

The objective of this study was to evaluate the efficacy of 40% glucose gel compared with infant formula in the treatment of early asymptomatic hypoglycemia in newborns with risk factors.

Patients and Method

Randomized clinical trial (RCT). Equivalence or non-inferiority evaluation study conducted at the Neonatology Service of the *Hospital Privado de Sur* (HPS), in Bahía Blanca, Argentina, between July 1º 2017, and June 30, 2020 (36 months). All NBs seen in the mother/child joint hospitalization wing, with risk factors for developing asymptomatic NH in the first 48 h of life were included. Inclusion criteria were: 1) term NB (37 to 41 weeks 6/7 days: child of a diabetic mother (CDM) treated with insulin or oral hypoglycemic agents; small for gestational age (SGA: < P10) and large for gestational age (LGA: > P90) according to Argentine population references[15-16]; 2) late preterm NB (35 to 36 weeks 6/7 days). Exclusion criteria were: 1) newborns admitted to neonatal care units, 2) newborns with oral mucosal disorders that prevented the gel administration, 3) newborns with clinical signs compatible with hypoglycemia or glycemia less than 25 mg/dL, confirmed by serum determination, and 4) refusal of their parents to participate in the study.

After a pilot test, with the consensual methodology and training of the personnel in charge of the study, the incorporation of cases in both groups was initiated.

Intervention

All newborns are placed in skin-to-skin contact in the first hour of life and subsequently receive breastfeeding on demand. In the reception room, informed

consent was given to the relatives of the newborns who met the inclusion criteria. Once the consent was accepted, the patients were selected, according to a simple randomization table drawn up "*ad hoc*", to receive 40 % glucose gel 0.5 ml/kg in the oral mucosa (Group A) or infant formula (starter formula) 9 ml/kg by syringe suction (Group B)[17]. The proposed intervention covered the first 48 h of life.

The newborns admitted to the study started the first glycemic measurement at two hours of life. In this first measurement, the cut-off value was set at 35 mg/dL. Lower values were reconfirmed by the central laboratory of the hospital. The presence of hypoglycemia indicated treatment according to the assigned group: 40% glucose gel (Group A) or infant formula (Group B). Successive measurements were established at one hour in case of hypoglycemia (cut-off value 47 mg/dL) or every 2 h in case of normal values. The maintenance of blood glucose levels above the established cut-off value extended the serum measurements to 12, 24, and 36 hours of life.

Failure was considered when the NB persisted with hypoglycemia in two consecutive or three alternating measurements after the indicated treatment twice. The intervention proposed in this study covered the first 48 h of life.

In the case of therapeutic failure, a neonatologist evaluated the approach to be followed according to the condition of the NB (sensorium, attitude, sucking, thermoregulation). In the absence of pathological clinical signs, infant formula was administered to both groups, and if hypoglycemia recurred, intravenous correction was indicated; in both cases without interrupting breastfeeding.

Administration of the gel: the dose was divided into halves and applied by nursing personnel to the oral mucosa (inner face of both cheeks) in a gentle massage, using biosafety gloves (Figure 1). The preparation of 40% glucose gel was carried out in the Institution's pharmacy as a costumised medication; it was replaced every two weeks.

Administration of infant formula: procedure carried out by nursing staff.

Preprandial blood glucose measurements were obtained by Accu-Chek® Active meter (Roche Laboratories), in the baby's room and measured in mg/dl.

Statistical analysis: The sample size was calculated in 306 NBs for each group. Hypothesis test for comparison of proportions, with power 0.90 to detect a difference of 0.05 when the proportions are approximately 0.95, considering alpha = 0.10. The Statgraphics Centurion XV software was used for data analysis.

The research protocol was approved by the Teaching and Research Committees of the HPS and Bioethics of the *Hospital Municipal "Leónidas Lucero"* of Bahía Blanca (date 6-15-2017). Informed consent was approved by the Legal Affairs Office of the HPS.

b

During the study period, 4,336 births were registered, and 866 (20 %) met the inclusion criteria (Table 1).

Metabolic measurements were performed in 782 neonates (90.2 %) (Figure 2). 278 (35.5 %) presented hypoglycemia. Two NBs were diagnosed with polycythemia and required hospitalization, as well as two NBs with blood glucose levels below 25 mg/dl (both children of diabetic mothers); 23 parents or caregivers (8.3%) refused to participate in the study and the NBs received infant formula for the correction of asymptomatic NH; the rest of those excluded[10] were due to errors in collecting or reading the samples.

A total of 241 NBs were included in the study, 118 (49 %) in Group A (glucose gel) and 123 (51 %) in Group B (infant formula). One NB in Group A presented clinical signs of hypoglycemia, requiring immediate intravenous correction. Follow-up was completed by 107 in Group A and 115 in Group B (Figure 2).

The neonates randomly assigned to each treatment constituted comparable groups for the evaluation of the efficacy of the treatments proposed for the correction of asymptomatic NH (Table 2).

In group A, 76 NBs (71 %) responded to treatment while 104 NBs (90.4 %) did so in group B, this difference being statistically significant (p-value < 0.001) (Table 3). The 95% confidence interval for estimating the difference in failure proportions between the two groups was [0.092555 - 0.295445].

The NBs who did not respond to the assigned therapy and required hospitalization for correction with intravenous glucose were similar in both groups, with 3/31 in group A and 2/11 in group B. (Table 3). Breastfeeding was maintained in all cases.

Table 4 describes the clinical characteristics of the NBs who did not respond to the therapy. The main risk factor in both groups was LGA. The time observed for therapeutic failure was mainly in the first 24 h (81%).

In the original protocol of the RCT, internal safety analysis of the results obtained with the participating methodologists (LG and MG) at the mid-term of the trial was established. However, the observations made by the intervening actors (nurses and physicians) hastened this analysis once the third part of the sample calculation had been obtained. The hypothesis test rejected the equality of failure proportions with a value of $p < 0.001$, concluding that, in order to reverse the results observed up to that moment and to be able to demonstrate that both treatments were equally effec-

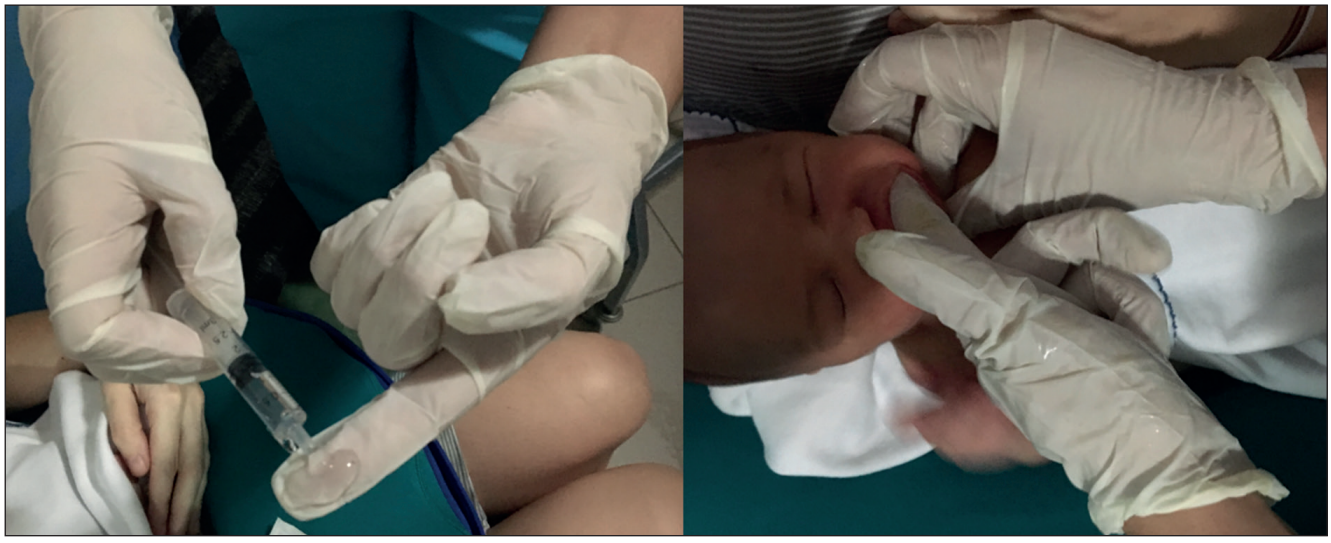

Figure 1. Administration of 40% glucose gel. Practice performed by nursing staff; the NB remains in the mother's arms.

tive, it would be necessary that in the next 200 NBs to be incorporated in each group, only 3 NBs should fail in group A.

Assuming the almost null probability of achieving these results, it was decided to discontinue the study, with the prior acceptance of the intervening committees.

Discussion

Attempting to demonstrate therapeutic interchangeability was the primary objective of this RCT. The non-equivalence between the administration of 40% glucose gel and infant formula for the correction of asymptomatic NH was the main finding.

Pediatricians and neonatologists are aware that NH is a preventable cause of brain injury[18]; it affects 10-15% of NBs and approximately half of at-risk NBs[19] and is associated with adverse sequels on many occasions[20]. It is of scientific interest to find effective therapies for its correction, without interfering with the mother-child relationship and breastfeeding.

With the commitment undertaken by the Institution as a "mother-child friendly hospital" since 1997[21], we decided to evaluate a therapeutic option to replace the administration of infant formula as initial therapy in the correction of asymptomatic NH. We did not find any reports in the literature that compared similar therapies used in our trial.

The work published by Harding J et al. from New Zealand, pioneers in the administration of glucose gel for the correction of asymptomatic NH, used placebo (0 mg of glucose) as the control group[12]; this is not a minor fact when analyzing their favorable therapeutic outcome. The bioavailability of carbohydrates and their route of administration could be related to the different therapeutic responses. An intake of 200 mg/kg of 40% glucose gel in the oral mucosa compared

Table 1. Characteristics of the population with risk factors for neonatal hypoglycemia

Newborns with risk factors for hypoglycemia	866/4336 (20%)
Sex	
Female	422 (48.7%)
Male	444 (51.3%)
Gestational age (weeks)	
Average	38.3
Median	38
Range	35 - 41
Birth weight (grams)	
Average	3500
Median	3740
Range	2060 - 4960
Risk factors	
LGA	531 (61.3%)
SGA	188 (21.7%)
Infant of a diabetic mother	37 (4.3%)
Late preterm	90 (10.4%)
Combinations	20 (2.3%)

LGA: Large for gestational age. SGA Small for gestational age.

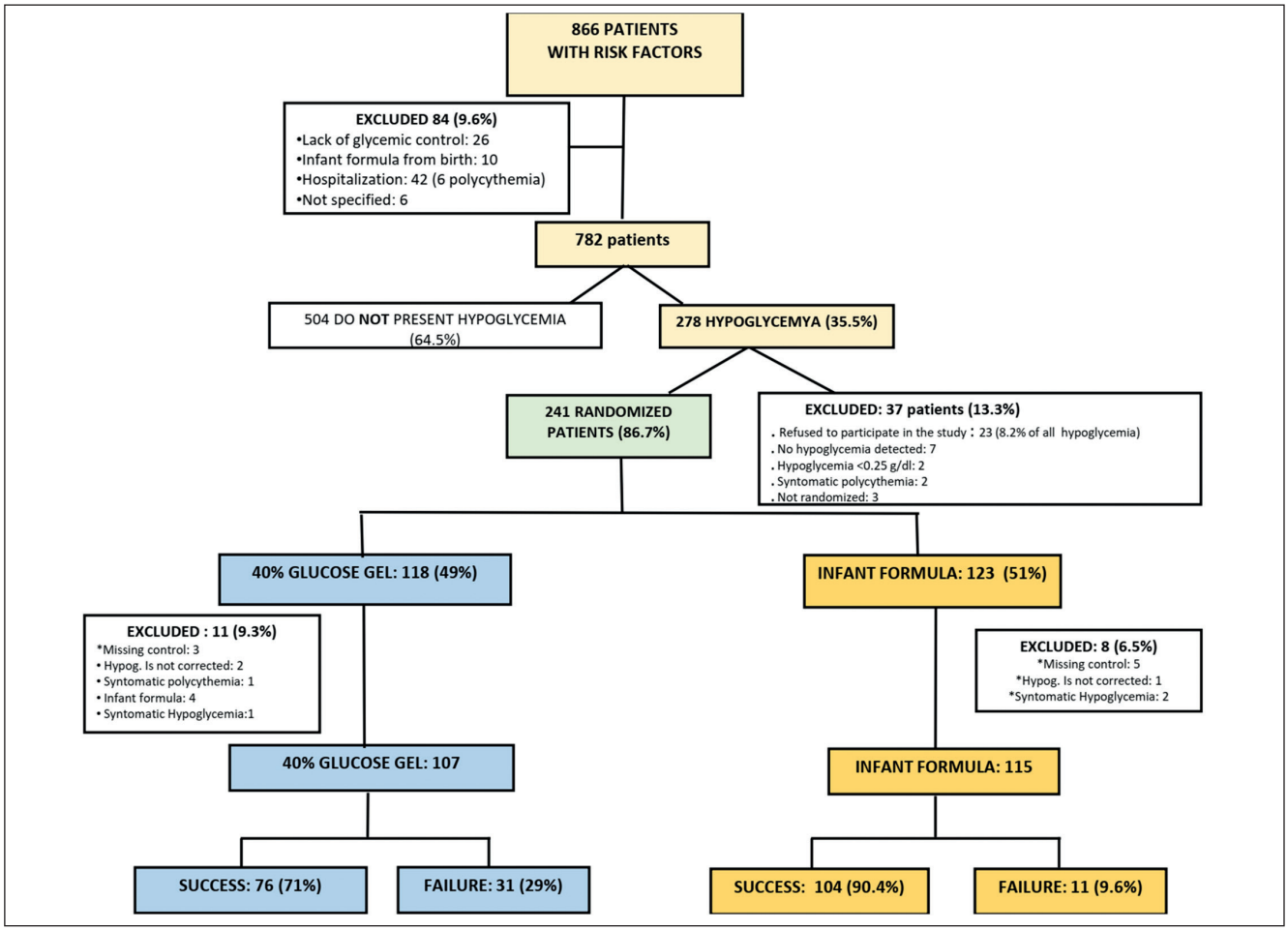

Figure 2. Studied population according to inclusion-exclusion criteria and randomized into Group A (40% Glucose gel) and B (Infant formula).

Table 2. Comparison of newborns analyzed according to treatment received (n: 222)

	40% Glucose gel	Infant formula	p value
Infants	107	115	
*Sex**			
Female	57 (25.7%)	56 (25.2%)	0.496
Male	50 (22.5%)	59 (26.6%)	
Risk factors			
SGA	23	26	0.581
LGA	63	65	0.927
Infant of diabetic mother	6	4	0.445
Late preterm	15	20	0.788
Birth weight (grams)	3399.28	3440.93	0.651
*Gestational age (weeks)**			
35	1 (0.5%)	0	0.362
36	14 (6.3%)	20 (9%)	
37	10 (4.5%)	14 (6.3%)	
38	32 (14.4%)	36 (16.2%)	
39	26 (11.7%)	32 (14.4%)	
40	22 (9.9%)	12 (5.4%)	
41	2 (0.9%)	1 (0.5%)	

*Percentages are expressed in relation to the total number of patients. LGA: Large for gestational age. SGA Small for gestational.

with 600 mg/kg with infant formula by enteral route, as in this trial, should not have an equivalent response.

Harris et al. describe a population of NBs at risk for asymptomatic NH with an incidence close to 50%, higher than that reported in this study (35.5%). Probably, the population's diversity is the cause of these findings. The risk groups for developing asymptomatic NB are similar in the different studies observed, including LGA, SGA (some include intrauterine growth restriction), children of diabetic mothers with their different classifications, and late preterm newborns (35-36 weeks 6/7).

The timing and duration of screening, as well as the threshold for brain injury remain uncertain. The lack of consensus among the different scientific societies in determining blood glucose values reflects the paucity of evidence on long-term outcomes following asymptomatic NH[3-5]. However, prospective follow-up of a 2-year cohort presented in the CHYLD study was not associated with adverse neurological outcomes in NBs ≥ 35 weeks with the proposed blood glucose values by the AAP (> 47 mg/dl - 2.6 mmol/L)[3,23].

Stewart et al. promote a multidisciplinary initiative ("Baby Friendly") for the correction of early hypoglycemia, with the use of glucose gel as the first line treatment; resulting in reduced use of infant formula and admissions to the neonatal unit, along with a parallel increase in breastfeeding at 3 months[24]. Harding J. et al. further extend its indication and recommend its preventive administration in late preterm or term newborns with aggravating factors[25].

Analytical errors in blood glucose determination, due to the diversity of operators involved, have probably been equally distributed in both groups[26]. Likewise, Solimano et al. reported different concentrations of glucose in commercial 40% gel preparations, another possible cause of error in the amount administered[27].

Deciding to discontinue a study under development is not a simple task; internal quality analyses make it possible to analyze failures and therapeutic futility and to continue with the trial, thus saving time and resources; in addition, the institution's committees facilitated the task[28].

Summarizing the strengths and weaknesses of this RCT, we can mention the lack of trials reported with similar therapeutic characteristics and the suspension of the trial when it was shown that there was no possibility of reversing the results, with the consequent low number of cases included. Perhaps we can add the lack of knowledge of undiagnosed gestational diabetes as a cause of NH in the newborn LGA.

Vain N and Vain-Chiarelli raise more doubts than certainties in the diagnosis and treatment of NH; they consider a possible overdiagnosis with invasive therapies in mostly healthy NBs[29,30]. It has been an open-ended story since its first publication in 1937 and has been ratified in recent decades[2,31-33].

In summary, despite not being able to demonstrate the equivalence of both therapeutic approaches in the correction of asymptomatic NH in late preterm or term NBs with aggravating factors, we believe that the

Table 3. Results according to treatment received

	40% glucose gel (107)	Infant formula (115)	p value
Responded to treatment			
Infants	76 (71%)	104 (90.4)	< 0.001
Hospitalized			
Infants	3/31	2/11	NS

Table 4. Characteristics of randomized NBs who failed the administered treatment

	40% glucose gel	Infant formula
N° de pacientes	31	11
Sex		
Female	14 (45.2%)	6 (54.5%)
Male	17 (54.8%)	5 (45.5%)
Gestational age (weeks)		
Range	36 - 41	36 - 40
Average	38.2	38
Median	38	38
Birth weight (grams)		
Range	2060 - 4140	2200 - 4290
Average	3332.5	3502.2
Median	3580	3710
Risk factors		
LGA	17 (54.8%)	7 (63.6%)
SGA	8 (25.8%)	1 (9.1%)
Late preterm	4 (12.9%)	2 (18.2%)
Infant of diabetic mother	2 (6.5%)	0
LGA + Infant of diabetic mother	0	1 (9.1%)
Moment of first hypoglycemia (hours of life)		
2	3 (9.7%)	0
4	8 (25.8%)	3 (27.2%)
12	11 (35.5%)	4 (36.4%)
24	1 (3.2%)	4 (36.4%)
36	7 (22.6%)	0
48	1 (3.2%)	0

GEG: grande para edad gestacional. PEG: pequeño para edad gestacional.

use of minimally invasive procedures that maintain the mother-child relationship in its broad concept and with controlled follow-up is necessary. The administration of 40% glucose gel is a simple, safe, and low-cost procedure; in fact, its administration was favorable in 71% of the NBs included in the study group, without requiring more hospitalization compared with the group that received infant formula.

Extensive multicenter protocols are needed to validate the use of glucose gel in low-risk populations with asymptomatic NH, avoiding undesirable dietary interference and separation of the mother-child binomial.

Conclusions

In this study, the administration of 40% glucose gel was not equivalent to the administration of infant formula for the correction of asymptomatic neonatal hypoglycemia in late preterm or term NBs with risk factors.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the parents (tutors) of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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