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OPTIMIZING NEONATAL HYPOGLYCEMIA MANAGEMENT: A PILOT RANDOMIZED CONTROLLED TRIAL OF A NOVEL PROTOCOL FOR INTRAVENOUS FLUIDS IN THE NICU

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ABSTRACT

The purpose of the study. Compared to Neonates with hypoglycemia should be treated according to the standard protocol, a new protocol is evaluated for safety. Methods. A pilot RCT with an open label. We included neonates who required intravenous fluids due to hypoglycemia during their stay in the NICU. An intervention group of 114 eligible neonates (glycemic control increased by 1.5%) and a standard protocol group (gastric emptying rate increased by 2 mg/kg/min) were randomly assigned. The primary aim of the study was to determine the Following enrollment in the study, the percentage of infants who developed hypoglycemia and hyperglycemia. Results. The initial GIR (6 ± 0 mg/kg/min versus 4.8 ± 1.4 mg/kg/min, P < 0.001), the mean maximum GIR (6.7 ± 1.6 mg/kg/min versus 5.6 ± 2 mg/kg/min, P = 0.03), the maximum concentration of glucose infused (13.8 ± 2.9% versus 10.9 ± 1.9%, P < 0.001), and the total amount of glucose infused in the intervention group, were significantly lower. Compared to the conventional protocol group where there were only five infants with hyperglycemia There was a significant difference between groups (n = 20, 39% versus n = 10, 16%, P = 0.07) in the mean maximum blood sugar levels (129x57 mg/dL versus 87x30 mg/dL, P = 0.001). When the highest and lowest recorded sugar concentrations were compared in the standard protocol group (median 93 mg/dL, IQR 52 to 147 mg/dL versus median 50 mg/dL, IQR 38 to 62.5 mg/dL, P = 0.03), significant differences were observed. Conclusion. Hypoglycemia in neonates can be managed effectively with a new and innovative algorithm, but this needs to be tested further before it is practiced routinely.

Key words: Neonatal hypoglycaemia, Glycemic control, Intravenous fluids, Randomized controlled trial.

INTRODUCTION

Hypoglycemia is defined as a drop in circulating glucose levels. The first description of hypoglycemia in children occurred almost 100 years ago, and newborns and older infants were diagnosed over 50 years ago [1]. One or more episodes of hypoglycemia are diagnosed in 23–50% of neonate in intensive care units [2–4]. The incidence of hypoglycemia was reported to be 9.6%, 15.3%, and 19.4%, respectively, in a study conducted in India [5]. In addition to adversely affecting the motor performance of babies born with hypoglycemia, it also adversely affects their IQ, reading ability, and arithmetic proficiency [6]. Thus, blood sugar should be corrected as soon as possible. In newborns or people with blood sugar levels below 30 mg/dL, symptomatic hypoglycemia is treated by bolusing 2 mL/kg of 10% dextrose and infusing 6 mg/kg/min glucose. It is currently the protocol in many units to gradually increase the glucose infusion rate (GIR) every 15-30 minutes if hypoglycemia persists [7, 8]. There are many calculations involved in this method, which results in a lot of time lags and errors in the preparation of fluids. The time lag and errors need to be reduced by a better method when implementing required GIR for neonatal hypoglycemia, as morbidities are related to the duration of hypoglycemia. Developing a new protocol and evaluating its safety for managing hypoglycemia in neonates compared to the study was conducted according to the standard protocol using an open-label, randomized controlled trial.

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METHOD AND MATERIAL

During An analysis of randomized pilot studies is presented here, patients were randomly assigned to one of several teaching hospitals in south India of tertiary level. A protocol for Institutional review board approval was obtained for this study at Fernandez Hospital. Parents consented before the infant was randomized in the study. A neonate who requires intravenous fluids for hypoglycemia was included in the inclusion criteria. Glucose levels under 40 mg/dL were considered hypoglycemic. In cases where intravenous fluids were required, intravenous fluids were considered

I. Lethargy, jitteriness, poor sucking, and seizures were symptoms of a symptomatic infant whose blood glucose was over 40 mg/dL.
II. Low blood glucose level, or
III. A fifteen-minute oral feed caused blood glucose levels to drop below 40 mg/dL.

I excluded sick neonates with hypoglycemia (Inotropes, ventilation, and oxygen are needed in shock, or intravenous fluids are already being administered for some other reason) and those who did not require Feeds to correct hypoglycemia (intravenously administered liquids), as well as those who could not obtain consent. Web based random number generators were used for randomization. A serially numbered opaque envelope concealed group allocation. A written consent was obtained and the outer cover of the envelope was filled out with the infant's details. Each envelope was opened by the principal investigator, and the babies were randomly assigned. Pre-designed case reporting forms were used to enter the necessary information after babies were assigned to intervention or standard protocol groups.

Standard Protocol

1. An infusion of 6 mg of glucose per kilogram per minute was started.
2. If blood sugar Infusion of glucose was increased by 2 mg/kg/min for 30 minutes while the blood glucose level remained below 40 mg/dL to a maximum of 14 mg/kg/min.
3. Glucose concentrations exceeding 12.5% for 12 hours were monitored with a central venous line.
4. Monitoring of blood glucose occurred 30 minutes after infusion started, 2 hours later, and every 6 hours thereafter if blood There was more than 50 mg of glucose in the blood. Every 30 minutes, monitoring was conducted until the blood sugar level exceeded 50 mg/dL if it was less than 50 mg/dL.
5. The GIR was tapered after two A blood sugar reading of 50 to 125 mg/dL every six hours if it is over 50 mg/dL but less than 125 mg/dL. Whenever the blood glucose was above 125 mg/dL, the tapering process was started right away. Two hours after taking the glucose, if it remained above 125 mg/dL, the tapering process was repeated immediately.
6. A taper of 1 mL/hour was performed if feeding had been started. For infants receiving 6 mg/kg/minute, the flow rate was 1 mL/hour; if continuing intravenous fluids, they were tapered to maintenance fluid. Tapering was performed every six hours for infants whose GIR was greater than Until 6 mg/kg/min is reached. Fluids were tapered off and feeding was started by 1 mL per hour once the GIR reached 6 mg/kg/min.

Intervention Group

1. Dextrose 10% was used to start the glucose infusion.
2. In this study, blood sugar level was increased in 1.5% increments every In the presence of elevated blood sugar levels, 30 minutes should be allowed (step 1 10% to 11.5% and step 2 11.5% to 13%). A switch to standard protocol was made if the baby's blood sugar remained below 40 mg/dL in two increments. A mixture of 10 mL 25% glucose and 90 mL 10% dextrose was prepared to produce 11.5% glucose. Whenever the glucose concentration increases by 1.5%, the Ten milliliters of 25% dextrose increase, and ten milliliters of 10% dextrose decrease.
3. As with the standard group, steps 3 through 5 were similar.
4. Glucose concentrations over 10% for infants were tapered by Each six hours, 1.5% is added. Glucose 10% for babies were introduced to feeds, tapering was done by 1mL/hour if they were still on intravenous fluids.

The blood sugar levels were monitored at admission, for 30 minutes, for two hours, and for six hours in both groups. In the case of sugar levels above Every 30 minutes, monitoring was performed at 50 mg/dL. A glucose level greater than 125 mg/dL required two-hour monitoring. Two mL/kg of 10% dextrose were given as a minibolus to all enrolled infants who were symptomatic or had sugars >30 mg/dL at enrollment. Feeding infants enteral nutrition did not involve using calorie supplements or glucose polymers. The amount of intravenous fluid administered to an infant was As determined by the weight of the infant and the date of birth his or her hydration status. A 12-hour period of full enteral feeding was required for neonates to exit the study.

The primary outcome measures included the Whether or not infants are hypoglycemic or hyperglycemic after feeding enrollment in the trial (defined as blood glucose Under 40 mg/dL or over 125 mg/dL). As secondary outcomes, we evaluated the mean maximal blood glucose, the average change in blood glucose between enrollment and discharge, whether a central line was required, what the GIR was, how fast the glucose was infused, how fast the insulin was infused, when enteral feeds were initiated, how fast they were initiated fully, and

how well the neurosonogram was performed upon discharge.

An Optium Xceed glucometer and glucose oxidase method were used to estimate blood glucose in venous blood samples. Regardless of the strip method, laboratory blood glucose results were always taken to confirm low or A blood sugar level of more than 125 mg/dL is considered to be high. Using an automated Hexokinase method, blood glucose levels were estimated in the lab.

Statistics

In the analysis of continuous variables, we used a Comparisons between groups should be made using Mann-Whitney U tests or Student's t-tests. Depending on the categorical variable, we used Student's t-tests and chi-square tests. When the P value was less than 0.05, it was considered significant was greater than 0.05. The study did not estimate the sample size a priori.

RESULTS

In this study, 57 infants participated. After the study was completed, all infants received their assigned treatment protocols. We found that 54 of the 114 participants had hypoglycemia as the result of intrauterine growth restriction (47%), 36 (31%) as the result of the mother having diabetes, 6 (5%) as the result of being large for gestation, and 18 (17%) were preterm. Table 1 shows that In terms of gestational age, birth weight, maternal risk factors, intrauterine growth status, or blood sugar levels, no significant differences were found between the two study groups at enrollment.

Table 1: Study groups' baseline variables are compared

Variables	**Standard protocol (*N* = 52); *n* (%)**	**Intervention protocol (*N* = 62); *n* (%)**	***P* value**
Gestation (mean ± SD)	2049 ± 514	2196 ± 878	0.45
Birth weight (g) (mean ± SD)	37.24 ± 3.4	37.04 ± 3.6	0.76
Male sex	19	25	0.55
GDM	9	11	1.00
1 min Apgar (median, IQR)	8	8	0.81
IUGR	15	14	0.43
Blood sugar at enrolment	28.8 ± 7.5	28.3 ± 8.4	0.42

Hypoglycemia Management

In the standard protocol group, 10 out of 52 infants had symptomatic hypoglycemia. Lethargy occurred in three infants, jitteriness in two, poor feeding in one, irritability in one, and seizures in one. Symptomatic hypoglycemia also occurred in five children in the intervention group. According to the frequency of the symptoms, jitteriness ranked third (n = 6), There were two cases of lethargy, two cases of poor feeding, and one case of seizures. There was a significant difference in the initial glucose infusion rate (6 mg/kg/min versus 4.8 mg/kg/min, P 0.001), a significant difference in the maximum glucose infusion rate (7.8 ± 2.7 mg/kg/min versus 6.7 ± 3 mg/kg/min, P = 0.03), a significant difference in glucose concentration (14.9 ± 3.9% versus 11.9 ± 2.9%, P < 0.001), and glucose infusion rates were significantly lower in the intervention group (average, IQR: 7.3 g/kg/day; 6.6-80% g/kg/day versus 6.2 g/kg/day; 5.3 to 7.3 g/kg/day, P = 0.005). GIR or dextrose increments were needed by the same proportion of infants in the two groups (n = 10, versus n = 16, P = 0.35). There were three infants in the intervention group who needed one in two infants who needed two glucose concentration increments (both to 13%), four glucose concentration increments (to 11.5%) were required, and three who needed three glucose concentration increments (or more). When glucose concentration needed each of the three infants received more than two increments of GIR 2 mg/kg/min higher before switching to standard protocol. A standard protocol group of two, two, and one infants required twice The maximum dose per minute is 10 mg/10 kg/min, twice that is 12 mg/12 kg/min, and more than three times that is 8 mg/kg/min. No difference was found between the standard protocol group and the intervention group in terms of the number of infants who required central lines (n = 12, 46 versus 6/18, P = 0.27).

Outcomes

Both groups had similar proportions of It was also observed that infants with low blood sugar (n = 10, versus n = 16, P = 0.35) and moderate low blood sugar (n = 28, versus n = 28, P = 0.63) were less likely to have hypoglycemia. The standard protocol group had a higher proportion of hyperglycemic infants in comparison with the low protocol group (n = 20, versus n = 10, P = 0.07). Standard protocol group had significantly higher mean sugar difference than nonstandard P = 0.03, median 50 mg/dL, IQR 38 to 62.5 mg/dL in protocol group versus median 93 mg/dL, IQR 52 to 147 mg/dL in non-protocol group. Neonatal hypoglycemia was the cause of one MRI abnormality in the intervention group, but it did not result in seizures or recurrences after enrollment. Hypoglycemia management did not contribute to the death of one infant dying from neonatal sepsis in the standard protocol group.

It took the IQR, 1 day versus 1 day versus 1–2.5 days, P = 0.60 for patients to initiate enteral feeding, and 1 day; 1–3.5 days for them to reach full enteral feeding, P = 0.62. There was no abnormality detected on neurosonograms at discharge for any of the infants enrolled in the study.

DISCUSSION

It was found that the standard protocol for treating hypoglycemia was as safe as the algorithm for managing hypoglycemia used in this pilot study. In both groups, a similar number of infants experienced hypoglycemia in the subsequent weeks. The new protocol is equally effective as Using the standard protocol, as the proportion of infants requiring increases in GIR was similar to that of infants requiring adjustments in GIR using the modified protocol increases in dextrose concentration in the intervention group. As a result, both groups took similar amounts of time to initiate oral feedings and to achieve full enteral feeding after enrollment. In spite of receiving less Daily GIR and glucose levels are lower, the effectiveness of the intervention group was similar. In addition to an increase in glucose requirements, Since this was a pilot study, three infants were switched from the intervention group into the standard protocol group.

A well-fasted neonate is estimated to have an endogenous glucose metabolism rate of between 4 and 6 mg/kg per minute. A 10% dextrose solution is used to achieve a GIR of 4 mg/kg per minute [9]. In this study, glucose stabilization in the intervention group can be explained by the starting mean GIR of In mg/kg/min, 4.8 x 1.4. 10% dextrose minibolus is recommended by the AAP at a dose of 2 mL/kg to newborns with severe and symptomatic hypoglycemia, and/or commencing If newborns have severe and symptomatic hypoglycemia, they should receive continuous infusions of 10% dextrose at 80-100 mL/kg per day. A workup for hyperinsulinemic hypoglycemia should be performed if plasma glucose does not reach 40 to 50 mg/dL After glucose infusion, within 24 hours. The guideline does not recommend increasing dextrose concentrations for hypoglycemia that occurs within 24 hours after starting glucose infusions. In Indian guidelines, miniboluses of 10% dextrose are recommended at a rate of 2 mL/kg per kg and glucose infusions are recommended at Minutely doses of 6 mg/kg. [7, 8] It is recommended to increase GIR by 2 mg/kg/min every 10 minutes after Hypoglycemia persists despite glucose infusion. It is recommended to administer A small dose of glucose is given followed by a glucose infusion at a rate of 6 to 8 mg/kg/min in a popular neonatal care manual. In cases where GIR is greater than 12 mg/kg/min, hyperinsulinemia must be evaluated [11]. Neonatal hypoglycemia and its management is not supported by evidence or consensus. A uniform protocol is provided for the first time in this study, which highlights these differences.

The median difference between the lowest and highest blood glucose in the standard protocol group was significantly higher. A standard protocol group also had a lower showed a tendency to experience hyperglycemic episodes more often. As compared to the standard protocol, the new protocol shows a 15% increase in GIR as opposed to the 33% increase based on the GIR increasing from As per standard protocol, the baseline dose is between 6 and 8 mg/kg/minute. When hypoglycemia occurs, cerebral blood flow increases compensatory to compensate and hyperglycemia decreases cerebral blood flow, and if this happens frequently, adverse effects may occur on the developing brain. High and fluctuating blood glucose levels are all part of the standard hypoglycemia management protocol need to be evaluated long term. One study by Vanhatalo and Tammela found that 16% of infants with hypoglycemia had episodes of hyperglycemia At a GIR of 8 mg/kg/min, 15% dextrose with 20% dextrose produced plasma glucose over 7.7 mmol/L (138 mg/dL).

In addition to short-term outcomes, long-term outcomes must be considered as well are adversely affected by hypoglycemia or hyperglycemia [6]. Study participants' long-term outcomes were not assessed.

Study Limitations and Merits

The study excluded infants with very severe diseases for ethical reasons. Given that the infants in the intervention group were returned to standard protocols, we are unable to explain why this protocol was effective in treating prolonged, refractory, or persistent hypoglycemia after 2 increments. In addition, this hypoglycemia correction protocol needs to be studied for its effect on an infant's long-term neurodevelopment.

In addition to the protocol, there are other formulas and methods of correcting neonatal hypoglycemia did not appear to be compared in the literature to others. This new protocol has several advantages are ease of preparation and reduced calculations. Dextrose infusions can be started more quickly and with fewer errors when calculations are less complicated. In addition to randomized trials on healthy babies, larger studies with sick neonates are this protocol must be tested to determine its efficacy.

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