Continuous Intragastric Dextrose: A Therapeutic Option for Refractory Hypoglycemia in Congenital Hyperinsulinism

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Established Facts

- Congenital hyperinsulinism is the most common cause of persistent hypoglycemia in infants and can be challenging to treat if not responsive to medical or surgical therapy.
- Neurodevelopmental outcomes are poor, likely related to hypoglycemia.
- If hypoglycemia persists despite medical or surgical management, a continuous supply of glucose, often given via supplemental enteral nutrition, may be necessary.

Novel Insights

- Our HI team uses dextrose solution given continuously via gastric tube to maintain euglycemia in infants with congenital hyperinsulinism who have persistent hypoglycemia despite medical or surgical management.
- Intragastric dextrose appears to be well-tolerated, with no change in WFL Z-score from baseline after a median follow-up of 11 months.
- Whether intragastric dextrose allows for improvement in oral feeding skills and earlier liberalization from enteral nutrition should be the focus of future study.

Keywords

Congenital hyperinsulinism · Hypoglycemia · Nutrition · Obesity · Intragastric dextrose · Octreotide

Abstract

Feeding problems are frequent in infants with congenital hyperinsulinism (HI) and may be exacerbated by continuous

enteral nutrition (EN) used to maintain euglycemia. Our center's HI team uses dextrose solution given continuously via gastric tube (intragastric dextrose, IGD) for infants not fully responsive to conventional medical therapy or pancreatectomy. Here, we describe our practice as well as growth, feed-

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ing, and adverse events in infants with HI exposed to IGD. **Methods:** This was a retrospective cohort of infants with HI treated with IGD from 2009–2017. Primary outcomes were weight-for-length and body mass index Z-scores (WFL-Z and BMI-Z) in the year following IGD initiation. Secondary outcomes included EN use and adverse events. We used multivariable regression to assess covariates of interest. **Results:** We studied 32 subjects (13 female) with a median age at IGD initiation of 73 days (range 17–367); median follow-up was 11.2 months (range 5.0–14.2). WFL-Z did not change significantly over time ($p > 0.05$). EN use decreased significantly over time, i.e., at 0 months: 72% (95% CI 53–85) vs. at 12 months 39% (95% CI 22–59). No potential adverse events led to discontinuation of IGD. **Conclusions:** Over a median follow-up of nearly 1 year, IGD was well-tolerated, with no change in WFL-Z or BMI-Z from baseline.

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Introduction

Congenital hyperinsulinism (HI), the most common cause of persistent hypoglycemia in infants and children, can be challenging to treat if therapy with diazoxide is ineffective or not tolerated. Despite the increasing awareness of HI, hypoglycemia-induced neurological impairment remains common [1, 2]. Aggressive management of recognized HI, therefore, is critically important to improve neurocognitive outcomes.

In a significant proportion of patients with HI, hypoglycemia must be addressed with alternative medications or therapies. Continuous enteral nutrition (EN) may effectively avoid hypoglycemia; however, it does not promote physiological oral feeding. At our Center for Congenital Hyperinsulinism, we routinely assess for and treat hypoglycemia that persists despite medical therapy and/or pancreatectomy. When limited fasting tolerance is identified, rather than continuous EN, we administer dextrose given continuously via nasogastric or gastrostomy tube to allow for home management. To our knowledge, no studies have described this therapeutic approach. In this report, we describe our practice, assess changes in growth and feeding during exposure to this therapy, and describe rates of reported adverse effects.

The Case Series

Setting and Study Population

In this retrospective cohort study, we included male and female infants with congenital HI treated at The Chil-

dren's Hospital of Philadelphia (CHOP) between 2009 and 2017, who were younger than 12 months of age at the time of dextrose initiation and remained on intragastric dextrose for at least 6 months. HI was defined using clinical criteria: at the time of hypoglycemia (<50 mg/dL) having detectable insulin, and/or suppressed beta-hydroxybutyrate, and/or suppressed free fatty acid plasma levels, and/or positive glycemic response to glucagon [3]. All subjects had weight and length measurements available at baseline and had these measurements available for at least 1 additional time point of interest (6 ± 2 months and/or 12 ± 2 months).

Intragastric Dextrose Therapy

All patients at CHOP treated with intragastric dextrose receive 20% dextrose solution; at discharge, this is provided by home care companies via premanufactured 500-mL sterile IV bags of 20% dextrose solution. Caregivers are instructed to withdraw and allocate into EN bags the amount of dextrose required per 24 h plus an additional 30 mL for priming the tubing (e.g., $6 \text{ mL/h} \times 24 \text{ h} = 144 + 30 \text{ mL} = 174 \text{ mL}$). The opened dextrose bag contents may be used within 28 days if refrigerated. We limit the dose of intragastric dextrose to a glucose infusion rate (GIR) of ≤ 10 mg dextrose/kg/min to avoid an excessively high osmotic load to the gut, which may be associated with poor absorption and intolerance. Thus, children with a higher GIR requirement are not candidates for this management approach. The duration and intervals of intragastric dextrose are determined by the efficacy of additional therapies in use, including octreotide; some patients require only overnight dextrose, bridging between an afternoon and morning octreotide dose, while others require continuous, 24-h dextrose support to maintain euglycemia between meals.

Methods

Our study was approved by the Institutional Review Board at CHOP. Informed consent was obtained from subjects' parents by phone. Parental phone interview was conducted by 3 investigators (M.E.V., M.C., and L.M.). Medical record review was used to identify outcomes of interest. For those subjects without complete follow-up at CHOP, records from treating pediatricians were obtained with parental permission for release of the medical records. Data were collected from the time of dextrose initiation and at 6 and 12 (± 2) months later. Phone interview was used to supplement details unavailable in the medical records, including perceived feeding difficulties, frequency of adverse events, and overall satisfaction with intragastric dextrose therapy.

Demographic and clinical characteristics are reported using standard descriptive statistics. Summary statistics are provided for the entire cohort. Due to the lack of a standard definition of excess adiposity in infants and toddlers younger than 2 years [4], we used 2 measures for our primary outcome: weight-for-length (WFL) >85th percentile and body mass index (BMI) >85th percentile on WHO growth charts [5, 6]. Additionally, BMI Z-score (BMI-Z) reflects standardization by age, while WFL Z-score (WFL-Z) does not. We used paired *t* tests to assess for differences in WFL-Z or BMI-Z between the time points 0, 6, 12 months. We also report weight and height Z-scores for each time point. To account for intrasubject correlation of measurements over time while adjusting for potential confounders, we used multivariable quasi-least squares (QLS) regression, a computational approach for estimation of correlation parameters in the framework of generalized estimating equations (GEE) [7]. Unlike GEE, QLS allows for the application of the Markov correlation structure, which accounts for unequally spaced data, as is true in our cohort's time of dextrose exposure. For the QLS model, Markov and autoregressive correlation structures were tested to model decreasing correlation with increasing separation in time of measurements.

In the final QLS model, Markov correlation structure was chosen as the working correlation structure using the adjusted quasi-likelihood information criterion (QIC), analogous to the adjusted Akaike's information criterion (AIC) for GEE, which is used to compare models fitted using maximum likelihood [8]. Covariates for multivariable models were included if the *p* value in the univariable regression was <0.1, or if the covariate was of explanatory interest. Backward elimination was used to determine the final multivariable model, allowing for only covariates of explanatory interest (months on dextrose) or those with a *p* value <0.05. Two-sided hypothesis tests were used throughout. *p* < 0.05 was considered statistically significant.

Secondary outcomes included change in EN use, as evaluated using the χ^2 test, and frequency of adverse events while managed with IGD. Oral feeding difficulties, defined as the need for tube feedings or attendance at feeding clinic, speech therapy, or parental report of such difficulties at baseline and at 12 months were compared using the χ^2 test. Proportions of subjects who experienced adverse events, including hypoglycemia, hyperglycemia, edema, vomiting, diarrhea, and feeding tube or pump malfunction, dislodgment, or failure, were determined from chart review and phone interview and are reported with 95% confidence intervals (CI).

Results

Patient Characteristics

Our cohort included 32 subjects (13 females). Median gestational age was 38 weeks (range 26–40); 5 subjects were born before 35 weeks' gestation. One subject discontinued IGD 3 days before the 6-month measurement, and 4 discontinued IGD between 6 and 12 months. Three subjects discontinued IGD between 6 and 12 months due to resolution of hypoglycemia: one had Kabuki syndrome, another had suspected stress-induced HI, and a third

Table 1. Cohort characteristics

Number of subjects (% female)	32 (41%)
Age at dextrose initiation, days	73 (17–367)
Duration of dextrose use, months	11.2 (5.0–14.2)
Gestational age, weeks	38 (26–40)
Mean birth weight (SD), kg	3.8 (1.0)
Mean birth weight Z-score (SD)	+0.85 (2.1)
Mean birth length (SD), cm	49.8 (6.3)
Mean birth length Z-score (SD) ^a	+0.87 (2.5)
Race/ethnicity	
Caucasian	19 (59)
Black	4 (13)
Asian	1 (3)
Other/not defined	8 (25)
Hispanic	7 (22)
Non-Hispanic	25 (78)
Genetic mutation	
ABCC8	22 (69)
KCNJ11	4 (13)
GCK	1 (3)
Negative	5 (16)
Syndrome	
Beckwith-Wiedemann	3: <i>KCNJ11</i> , <i>ABCC8</i> , and no mutation
Turner	1: no mutation
Pancreatectomy	18 (56)
Supplemental enteral nutrition at baseline	23 (72)

Values are expressed as *n* (%) or median (range), unless otherwise stated.

^a Available for 19 infants.

had a known recessive maternal *KCNJ11* (c.844G>A, p.Glu282Lys) mutation and a paternal *ABCC8* (c.3403–69C>T) variant of unknown significance. One subject with compound heterozygous mutations in *ABCC8* (c.208G>A, p.Gly70Arg [maternal] and c.382G>T, p.Glu128X [de novo]) was started on octreotide, and one with genetics-negative HI no longer required IGD after lanreotide and diazoxide dose increases.

Genetic evaluation was available for all subjects; 26 had HI due to inactivating mutations in a gene encoding a potassium-ATP channel subunit (22 *ABCC8*, 4 *KCNJ11*). Three subjects had Beckwith-Wiedemann syndrome (1 with mutation in *ABCC8*, 1 in *KCNJ11*, and in 1 genetic testing for HI-related genes was negative), and 1 had Turner syndrome (HI genetics-negative). These subjects were excluded from growth analyses due to the anticipated differential growth patterns. The vast majority (25/32) had diffuse disease. Slightly more than half (18/32) underwent pancreatectomy. The majority required sup-

Table 2. Univariable and multivariable regression for WFL and BMI Z-scores at follow-up ($n = 28$)

	Univariable		Multivariable	
	coefficient (95% CI)	<i>p</i> value	coefficient (95% CI)	<i>p</i> value
Outcome: WFL Z-score				
Baseline WFL Z-score	0.63 (0.39–0.87)	<i><0.0001</i>	0.58 (0.34–0.82)	<i><0.001</i>
Enteral nutrition	0.76 (0.04–1.48)	<i>0.039</i>	0.78 (0.16–1.40)	<i>0.014</i>
Months of dextrose	0.01 (–0.05 to 0.08)	0.7	0.02 (–0.04 to 0.09)	0.5
Gestational age (weeks)	–0.13 (–0.25 to –0.01)	<i>0.028</i>		
Female sex	0.07 (0.94 to 1.08)	0.9		
Pancreatectomy	0.86 (–0.17 to 1.90)	0.102		
K _{ATP} mutation	1.67 (0.70–2.65)	<i>0.006</i>		
Constant			0.09 (–0.82 to 1.00)	0.8
Outcome: BMI Z-score				
Baseline BMI Z-score	0.61 (0.39–0.83)	<i><0.0001</i>	0.57 (0.33–0.82)	<i><0.001</i>
Enteral nutrition	0.71 (–0.01 to 1.44)	0.05		
Months on dextrose	0.03 (–0.04 to 0.10)	0.4	0.002 (–0.58 to 0.06)	0.96
Gestational age (weeks)	–0.16 (–0.27 to –0.05)	<i>0.003</i>	–0.12 (–0.19 to –0.04)	<i>0.003</i>
Female sex	0.04 (–0.3 to 1.01)	0.9		
Pancreatectomy	0.77 (–0.25 to 1.78)	0.14		
K _{ATP} mutation	1.60 (0.67–2.52)	<i>0.001</i>		
Constant			5.06 (2.08–8.05)	0.001

Values in italics denote statistically significant findings (p value <0.05).

Fig. 1. Weight-for-length (WFL) and body mass index (BMI) Z-scores at each follow-up time point for subjects who remained on dextrose. Neither WFL Z-score nor BMI Z-score changed significantly over time.

plemental EN at baseline (23/32). Approximately 1/3 (11/32) were on octreotide at baseline. Median age at dextrose initiation was 73 days of life (range 17–367 days). For our cohort overall, the median duration of dextrose exposure at the time of the final body size measurement was 11.2 months (range 5–14.2). Table 1 displays a summary of patient characteristics.

Nutritional Status and Growth

At baseline, mean WFL-Z was 1.14 (SD 1.53) and BMI-Z was 0.96 (SD 1.67). Forty-eight percent (95% CI 30.1–66.9%) were overweight, as defined by WFL-Z $> +1.04$ or BMI-Z $> +1.04$. WFL-Z and BMI-Z did not differ between baseline and 6 months, baseline and 12 months, or 6 and 12 months ($p > 0.05$ by paired t tests). At baseline, mean weight Z score was 0.48 (SD 1.71), and mean height Z score was -0.36 (SD 1.62). Baseline WFL-Z or BMI-Z and supplemental EN were significant in both univariable regression and when included in the adjusted model. Gestational age was significantly associated with lower WFL-Z and BMI-Z at follow-up in the univariable regression. As shown in Table 2, the final QLS regression model confirmed the lack of change in WFL-Z over time (coefficient for months of dextrose exposure = 0.02, $p = 0.6$). Baseline WFL-Z was positively associated with follow-up WFL-Z (coefficient = 0.62, $p < 0.001$). Use of EN in addition to intragastric dextrose was associated with a higher WFL-Z (coefficient = 0.81, $p = 0.009$). Similarly, multivariable QLS regression confirmed the lack of change in BMI-Z over time (coefficient for months of dextrose exposure = 0.002, $p = 0.96$). Like WFL-Z, baseline BMI-Z was positively associated with follow-up BMI-Z (coefficient = 0.57, $p < 0.001$). Unlike WFL-Z, the use of EN was not as-

Table 3. Cohort characteristics by month of dextrose exposure

	Approximate month of follow-up		
	0	6	12
<i>Growth evaluation</i>			
Subjects, <i>n</i>	29	26	23
Mean weight Z-score (SD)	+0.48 (1.71)	+0.78 (1.43)	+0.96 (1.53)
Mean length Z-score (SD)	−0.36 (1.62)	−0.10 (1.23)	−0.08 (1.28)
Mean WFL-Z (SD)	+1.14 (1.53)	+1.13 (1.50)	+1.30 (1.40)
Mean BMI-Z (SD)	+0.96 (1.66)	+1.12 (1.50)	+1.35 (1.31)
Overweight by WFL-Z > +1.04 (95% CI)	48% (30–67%)	65% (44–82%)	52% (31–73%)
Overweight by BMI-Z > +1.04 (95% CI)	48% (30–67%)	65% (44–82%)	52% (31–73%)
<i>Secondary outcomes</i>			
Subjects, <i>n</i>	32	28	25
Enteral nutrition (95% CI)	72% (53–85%)	58% (39–75%)	39% (22–59%)
Feeding difficulties (95% CI)	31% (17–50%)	36% (20–55%)	36% (20–56%)

WFL-Z, weight-for-length Z-score; BMI-Z, body mass index Z-score.

sociated with BMI-Z in the multivariable model. In addition, unlike WFL-Z, BMI-Z remained significantly negatively associated with gestational age (coefficient = −0.012, $p = 0.003$). Subjects born before 35 weeks' gestation were excluded in a sensitivity analysis to further assess growth over time; the strength and association of our findings were unchanged (online suppl. Table 1; see www.karger.com/doi/10.1159/000491105 for all online suppl. material). Figure 1 demonstrates the WFL-Z and BMI-Z at dextrose initiation and at 6 and 12 months of follow-up for those who remained on dextrose.

Nutrition and Feeding Difficulties

As shown in Table 3, frequency of supplemental EN use decreased during follow-up ($p = 0.006$; baseline: 72% [95% CI 53–85%]; 12 months: 39% [95% CI 22–59%]). Documented or reported presence of feeding difficulties or use of speech therapy did not change over time ($p = 0.7$; baseline: 31% [95% CI 17–50%]; 12 months: 34% [95% CI 19–53%]).

Adverse Events

Table 4 displays the frequency of reported adverse events, including hypo- and hyperglycemia, fluid overload/edema, vomiting, diarrhea, and tube or pump malfunction or dislodgment. Parental report and rates recorded on medical charts were roughly equivalent for each measure, with the exception of hypoglycemia and hyperglycemia. Hypoglycemia while managed with IGD

Table 4. Adverse events while on dextrose

Adverse event	Parental report (<i>n</i> = 21)	Medical chart (<i>n</i> = 32)
Vomiting ¹	33.3%	28.1%
Diarrhea ¹	4.8%	9.4%
Hypoglycemia <70 mg/dL	71.4%	31.3%
Hyperglycemia >150 mg/dL	57.1%	15.6%
Tube/pump malfunction or problems	57.1%	68.8%
Edema	0.0%	3.1%

¹ Parents reporting a frequency of more than once a week; documented on the chart as present/absent.

was documented on the medical chart for 13/32 (31.3%) subjects. In 3 cases, octreotide was initiated or dose increased as a result. In one, IGD dose increase was documented, with resolution of hypoglycemia. In the remainder, hypoglycemia was transient in the setting of illness.

Parental Experience

Using a 5-point Likert scale to rate overall experience with intragastric dextrose use at home, 65% of parents were “satisfied” or “very-satisfied,” 20% were “unsure,” and 15% were “dissatisfied” or “very dissatisfied.”

Discussion

Our data suggest that the use of intragastric dextrose for the management of persistent hypoglycemia in infants with congenital HI is safe and well-tolerated overall. This therapy offers the option of ad lib oral feeding without concern for frequent hypoglycemia due to limited fasting tolerance, perhaps lessening feeding aversion. Our study's strengths include the relatively large cohort of infants with congenital HI described, the standardized approach by the HI treatment team at our specialized center, and the first description of the use of intragastric dextrose in practice, combined with growth data over 1 year of follow-up. Limitations include the retrospective design and limited ability to capture potential adverse events.

Obesity

To avoid excessive caloric intake, our nutritionists work with families to develop balanced feeding plans that take intragastric dextrose into account. To assess the success of this attempt, we evaluated the change in WFL-Z and BMI-Z after several months of infants receiving dextrose in addition to feeds. Our results demonstrate no significant change in WFL-Z or BMI-Z over a median follow-up period of 11.2 months. Although reassuring, the effect on growth of longer-term dextrose use in later childhood is unknown. In this retrospective cohort, we were unable to obtain caloric intake estimates to correlate with growth. In addition, our assessment of nutritional status relied on anthropometric data, rather than body composition. It is possible that body composition, including fat and lean mass, changed over the follow-up period despite stable WFL-Z and BMI-Z.

Weight gain during early infancy has been associated with childhood obesity, even in the first months of life [9, 10], emphasizing the importance of minimizing future harm by avoiding unnecessary caloric burden in this population. In addition, as approximately 1/3 patients who undergo near-total pancreatectomy develop diabetes immediately after surgery [1], the risk of insulin resistance secondary to obesity may worsen glycemic control. Our findings demonstrate no change in WFL-Z or BMI-Z over time with dextrose exposure, but our cohort had high WFL-Z and BMI-Z at baseline, with half of the subjects with these high scores being defined according to the WHO criteria.

Although our cohort included only patients who received intragastric dextrose without a control group, a previous study by Banerjee et al. [11] suggested that

among children not treated with intragastric dextrose, weight- and length-for-age SDS at 6- and 12-month follow-up do not increase or decrease significantly compared to baseline. The population they describe included a large proportion receiving EN, similar to our cohort. Future studies to evaluate a comparison group of infants with congenital HI with similar rates of pancreatectomy and K_{ATP} mutations are needed to better define the role of intragastric dextrose in growth over time.

Enteral Nutrition

Significantly fewer patients used EN at 6 and 12 months than at baseline. Our relatively high rate of baseline feeding problems compared to prior cohorts [11, 12] may be related to the enrichment in more severe HI, with ongoing hypoglycemia despite medication or surgery. Our study did not assess neurodevelopmental status, which has been associated with feeding difficulties [13]. However, in a cohort of children with congenital HI described by Al-Shanafey and Alkhudhur [12], feeding aversion was similarly common among both developmentally delayed and nondelayed patients. As described above, there was no significant change in reported presence of feeding difficulty or use of speech therapy over time. This is notable, as even in the presence of intragastric dextrose use, the likelihood of developing dependence on EN was not increased.

Adverse Events

We assessed adverse events of interest, including hypo- and hyperglycemia, frequency of vomiting, diarrhea, and tube or pump difficulties, by means of parental report and medical record review, in an attempt to address recall bias and to enrich the data available on chart review. Overall, tube or pump malfunction was common in both parental report and documented medical histories; it is unknown whether this was specifically related to the intragastric dextrose or supplemental EN. There were no significant concerns for fluid overload edema during the follow-up period. Gastrointestinal problems, including vomiting or diarrhea, were relatively frequent both by parental report and as documented, but intragastric dextrose was not discontinued in those who reported these potential adverse effects. Hypoglycemia was reported by parents at high rates, which may reflect recall bias, as hypoglycemia significant enough to warrant consultation with the medical team was present at much lower rates. Nevertheless, the persistence of hypoglycemia despite continuous dextrose supply highlights the need for more definitive and effective therapies for this population.

Conclusions

Intragastric dextrose for the management of persistent hypoglycemia despite medical and surgical therapy among infants with congenital HI appeared to be safe and did not lead to significant changes in BMI-Z or WFL-Z over a median of 11 months of follow-up. Despite the potential inconvenience of the therapy for families, 65% were satisfied or very satisfied with the therapy. Of great interest is the neurodevelopmental outcome of these patients, as the goal of intragastric dextrose is to lessen exposure to hypoglycemia. This was not a focus of our study, but should be evaluated in future studies.

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