JIMD Reports
DOI 10.1007/8904_2018_140

RESEARCH REPORT

The Effect of Continuous Intravenous Glucagon on Glucose Requirements in Infants with Congenital Hyperinsulinism

Colin P. Hawkes · Juan J. Lado · Stephanie Givler · Diva D. De Leon

Received: 19 June 2018 / Revised: 17 August 2018 / Accepted: 28 August 2018 / Published online: 12 October 2018

Abstract *Background/Aims*: Continuous intravenous glucagon is frequently used in the management of severe congenital hyperinsulinism (HI), but its efficacy in these patients has not been systematically evaluated. The aim of this study was to describe the use of continuous intravenous glucagon and to evaluate its effect on the glucose infusion rate (GIR) requirement in infants with HI.

Methods: Retrospective chart review of children with HI who received continuous intravenous glucagon for prevention of hypoglycemia at the Children's Hospital of Philadelphia between 2003 and 2013.

Results: Forty (22 male) infants were included, and median (IQR) age at glucagon treatment was 29 (23, 54) days. Median glucagon dose was 205 (178, 235) mcg/kg/day and duration of treatment was 5 (3, 9) days. GIR reduced from 18.5 (12.9, 22.8) to 11 (6.6, 17.5) mg/kg/min 24 h after starting glucagon ($p < 0.001$), and hypoglycemia frequency reduced from 1.9 (1.3, 2.9) to 0.7 (0.3, 1.2) episodes per day. Vomiting ($n = 11$, 13%), rash ($n = 2$, 2%), and respiratory distress ($n = 15$, 19%) were seen during glucagon treatment.

Conclusion: An intravenous glucagon infusion reduces the required GIR to maintain euglycemia, decreasing the risks associated with the administration of high fluid volume or fluids with high-glucose concentrations.

Abbreviations

GIR	Glucose infusion rate
HI	Hyperinsulinism
K_{ATP}	ATP-sensitive potassium channel

Introduction

Congenital hyperinsulinism (HI) is a common cause of persistent hypoglycemia in infants and children. This condition is characterized by dysregulated insulin secretion, and delayed treatment is associated with severe hypoglycemia with increased risk of seizures, developmental delay, and permanent brain injury (Palladino and Stanley 2011; Meissner et al. 2003; Steinkrauss et al. 2005; Lord et al. 2015). Causal mutations in eleven genes have been described in congenital HI, with the most severe forms of disease seen in individuals with inactivating mutations affecting the ATP-sensitive potassium channel (K_{ATP}) (Vajravelu and De Leon 2018). However, approximately 50% of infants with congenital HI do not have an identified genetic cause of disease (Lord et al. 2013; Lord and De Leon 2013).

Available medical treatments for the management of infants with HI are limited. Currently, two medications are routinely used to suppress insulin secretion and ameliorate hypoglycemia in these infants: diazoxide, a K_{ATP} channel activator that maintains the channel in the open state, and octreotide, a somatostatin analog (Lord and De Leon 2013). For children with severe HI, medical management can be

Colin P. Hawkes and Juan J. Lado contributed equally to this work.

Communicated by: Gerard T. Berry, M.D.

C. P. Hawkes · S. Givler · D. D. De Leon (✉)
Division of Endocrinology and Diabetes, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
e-mail: deleon@email.chop.edu

C. P. Hawkes · D. D. De Leon
Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

J. J. Lado
Division of Pediatric Endocrinology, Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA

ineffective in preventing hypoglycemia and pancreatectomy may be required (Lord et al. 2013). Prior to pancreatectomy, these children require a continuous glucose infusion at high concentrations and often at high fluid volumes. Central venous access may be required to deliver high concentrations of intravenous dextrose, which may be associated with increased risk of infection and intestinal ischemia (Hawkes et al. 2016; Barrington 2000). Increased intravenous fluid volumes in neonates can result in fluid overload and cardiac failure, which can also be exacerbated by diazoxide administration (Lord and De Leon 2013). Glucagon is often used to reduce glucose demands and consequently can reduce these risks in infants with congenital HI (Palladino and Stanley 2011; Lord et al. 2013).

Glucagon opposes insulin action (Quesada et al. 2008) and prevents hypoglycemia by stimulating hepatic gluconeogenesis and glycogenolysis, as well as inhibiting glycogen synthesis and hepatic glucose uptake. Glucagon can also stimulate the uptake of amino acids in the liver as well as increase the release of glycerol from adipocytes, both of which can be used for gluconeogenesis [reviewed in (Unger and Cherrington 2012)]. Despite widespread use of intravenous glucagon in congenital HI, the only published reports describing its use have been in neonates with unspecified hypoglycemia (Charsha et al. 2003; Miralles et al. 2002; Carter et al. 1988). There have been concerns raised regarding a possible association between glucagon treatment and thrombocytopenia or hyponatremia (Belik et al. 2001), but thrombocytopenia was not seen in these retrospective studies including 108 infants, and hyponatremia was considered to be related to excess fluid administration (Charsha et al. 2003; Miralles et al. 2002; Carter et al. 1988).

The aim of this study was to determine the effect of intravenous glucagon on the required glucose infusion rate (GIR) in infants with severe HI awaiting surgical management of their disease. As a secondary outcome, we sought to describe the rates of adverse events seen in infants during glucagon infusion.

Methods

A retrospective chart review of infants with HI who were treated with a continuous intravenous glucagon infusion prior to partial or subtotal pancreatectomy between January 2003 and December 2013 at the Children's Hospital of Philadelphia was conducted. The Institutional Review Board at The Children's Hospital of Philadelphia approved this study.

All infants with a diagnosis of focal or diffuse HI who subsequently underwent pancreatic surgery were eligible for inclusion in this study if they were under 6 months of age at the time of glucagon treatment, they received glucagon for greater than 24 h, and glucose measurements in the 24 h prior to glucagon treatment were available. All children treated with glucagon, regardless of age and availability of glucose measurements, were included in the analysis of adverse events during glucagon treatment.

The diagnosis of HI was based on biochemical evidence of insulin excess at the time of plasma glucose <50 mg/dL, as previously described (Ferrara et al. 2016). The time of glucagon initiation was extracted from the electronic health record. Capillary glucose concentrations were monitored during glucagon treatment at least every 3 h, using a point-of-care glucose meter [Lifescan SureStep Pro (Johnson & Johnson, PA, USA) prior to 2012 and Nova StatStrip (Novo Nordisk, Bagsvaerd, Denmark) after 2012].

Glucagon Administration

Glucagon was administered intravenously, either through a peripheral or a central intravenous line. For administration, glucagon was diluted in 5% dextrose to a concentration of 42 mcg/mL. The initial dose for all patients was 1 mg in 24 h, independent of body weight. To prevent precipitation, bags of diluted glucagon and infusion tubing were replaced with freshly prepared glucagon every 24 h.

Statistical Analysis

In analyzing the efficacy of glucagon infusion, the primary outcome was the GIR at 24 h before and after starting glucagon infusion. Secondary outcomes were the frequency of hypoglycemia (plasma glucose <70 mg/dL) and hyperglycemia (plasma glucose >140 mg/dL) in the days prior to and during glucagon treatment. The number of hypo- and hyperglycemia events was averaged for up to 4 days before and during glucagon treatment. Non-normally distributed continuous variables including GIR, hypoglycemia frequency, and hyperglycemia frequency before and during treatment were described using medians and interquartile ranges (IQR) and compared using Wilcoxon signed-rank test. Statistical analyses were performed using SPSS 22.0 (IBM, N.Y., USA). Figures were generated using Prism 5.0 (GraphPad Software Inc., California, USA) and Adobe Illustrator 16.0 (Adobe Systems Inc., California, USA).

Results

Eighty-seven children diagnosed with congenital HI were treated with continuous intravenous glucagon infusion prior to pancreatectomy at the Children's Hospital of Philadelphia between January 2003 and December 2013. Of these, 40 were eligible for inclusion in the analysis of

glucagon efficacy (7 were over 6 months of age, 31 commenced treatment with glucagon prior to transfer to our center, and 9 were treated with glucagon immediately on admission and did not have 24 h of glucose measurements available prior to treatment with glucagon). All 87 infants were included in the analysis of adverse events during glucagon treatment.

Efficacy of Glucagon Infusion in Children with Congenital HI

Of the 87 infants treated with intravenous glucagon, 40 had data available of glycemic control before and after glucagon treatment. The median (IQR) age at the time of starting glucagon treatment was 29 (23, 56) days of age, and duration of glucagon treatment was 5 (3, 9) days. Demographic and clinical data for these infants are shown in Table 1.

Of the 40 eligible children, 34 had a decreased glucose infusion rate (GIR) 24 h after starting glucagon treatment. Four children had an increased GIR, and two had no change. Intravenous glucose was completely stopped in two infants after starting glucagon. Overall, there was a statistically significant reduction in the median (IQR) GIR during the 24 h following initiation of continuous glucagon infusion compared to 24 h before initiation (18.5 (12.9, 22.8) to 11 (6.6, 17.5) mg/kg/min, $p < 0.001$) (Fig. 1). Starting glucagon was also associated with a reduction in the median (IQR) frequency of hypoglycemia (1.9 (1.3, 2.9) to 0.7 (0.3, 1.2) episodes per day, $p < 0.001$) (Fig. 2a) without a change in the frequency of hyperglycemia (0.8 (0.3, 1.9) to 1 (0.5, 1.7) episodes per day, $p = 0.3$) (Fig. 2b).

Adverse Events

Thirty-five of the 87 children (41%) treated with continuous glucagon infusion experienced adverse events during treatment. Multiple adverse events were reported during treatment. Vomiting ($n = 11$, 13%), rash ($n = 2$, 2%), and respiratory distress ($n = 15$, 19%) are reported side effects of glucagon treatment and were seen in these patients. One patient had thrombocytopenia prior to starting glucagon treatment, but no patient developed thrombocytopenia during glucagon treatment.

Discussion

Continuous intravenous glucagon is effective in the acute management of infants with congenital HI. We have shown

Table 1 Demographics and clinical characteristics

Characteristic	$n = 40$
Male	22 (55%)
Gestational age, weeks	38 (36, 39)
Age at starting glucagon, days	29 (23, 54)
Duration of glucagon treatment, days	5 (3, 9)
Glucagon dose, mcg/kg/day	205 (178, 235)
Concomitant medications	
Diazoxide[a]	0 (0%)
Octreotide	2 (5%)
Genetic mutations	
ABCC8	
Monoallelic	18 (45%)
Biallelic	15 (37.5%)
KCNJ11	
Monoallelic	3 (7.5%)
Biallelic	2 (5%)
None identified	2 (5%)
Pancreatic histology	
Diffuse	24 (60%)
Focal	14 (35%)
Other	2 (5%)

[a] All infants had failed a trial of diazoxide treatment prior to starting glucagon treatment

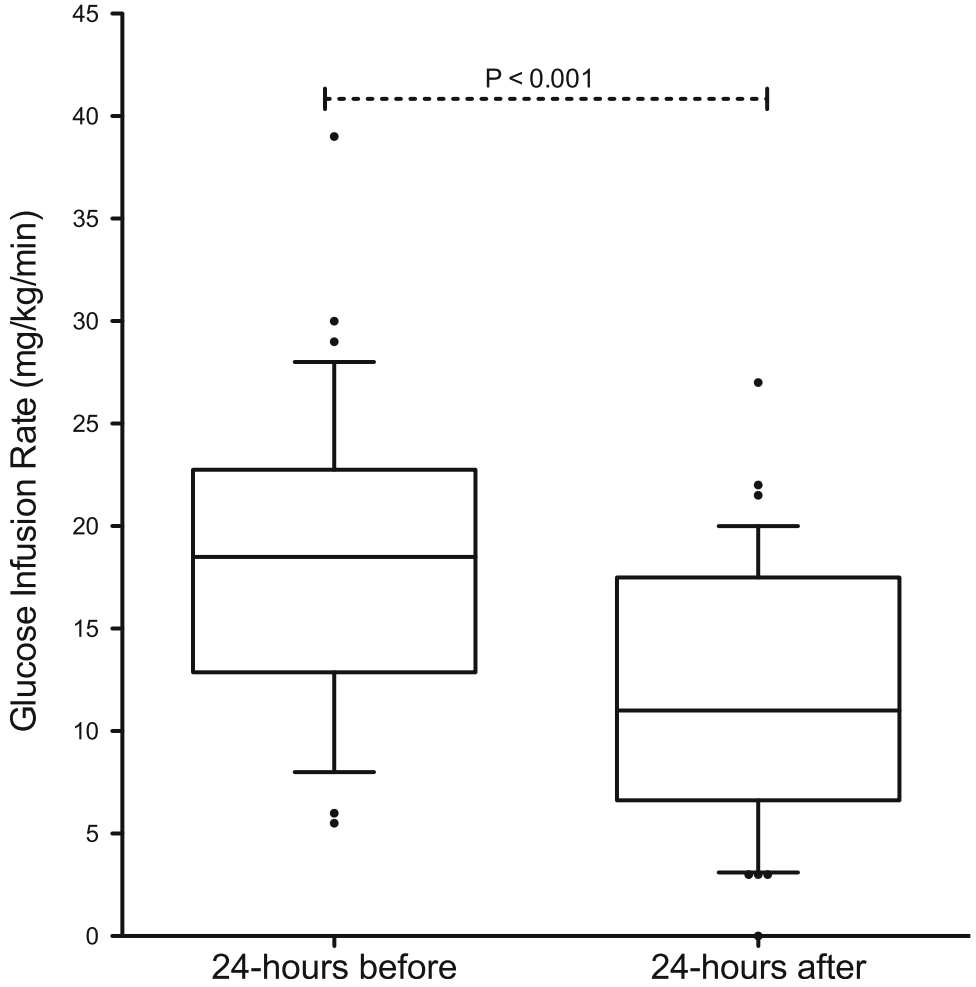

Fig. 1 Glucose infusion rate (GIR, in mg/kg/min) in children with congenital hyperinsulinism 24 h prior to and 24 h after starting continuous glucagon infusion. Box represents 25th and 75th percentiles, and whiskers represent 10th and 90th percentiles

that this treatment is associated with a median reduction in GIR of 7.5 mg/kg/min within 24 h of starting treatment and a significant reduction in the frequency of hypoglycemia without an increase in hyperglycemia. This reduction in GIR can reduce the need for hyperosmolar concentrated glucose or high-volume intravenous infusions. Although numerous adverse events were seen during glucagon treatment, it is not possible to determine if these are related to glucagon infusion, and we generally believe that this is a safe treatment in this population.

When compared with previous studies of glucagon infusion in infants with hypoglycemia, we have observed similar reductions in GIR and hypoglycemia during treatment. However, our study is the first to describe this only in infants with severe HI requiring surgical management. These infants are at particularly high risk of unfavorable developmental outcomes due to the severe and persistent hypoglycemia and often require extremely high concentrations of infused glucose to maintain euglycemia. In infants with congenital HI, endogenous glucagon secretion is blunted during hypoglycemia (Hussain et al. 2005), making exogenous replacement a physiologically appropriate treatment.

There have been concerns regarding the association between treatment of neonates with intravenous glucagon and the development of complications including hyponatremia and thrombocytopenia (Charsha et al. 2003; Miralles et al. 2002; Belik et al. 2001). In this study, we have evaluated the safety of glucagon infusion in the largest reported cohort of treated infants with HI. Only one child in this study had thrombocytopenia, but this was present prior to the initiation of glucagon infusion. Hyponatremia was not seen in any infant included in this study. Vomiting, rash, and respiratory distress are reported adverse effects that may be associated with glucagon administration (Food and Drug Administration n.d.) and, while these were seen in some of the patients included in this study, it is difficult to ascertain that this was associated with glucagon treatment.

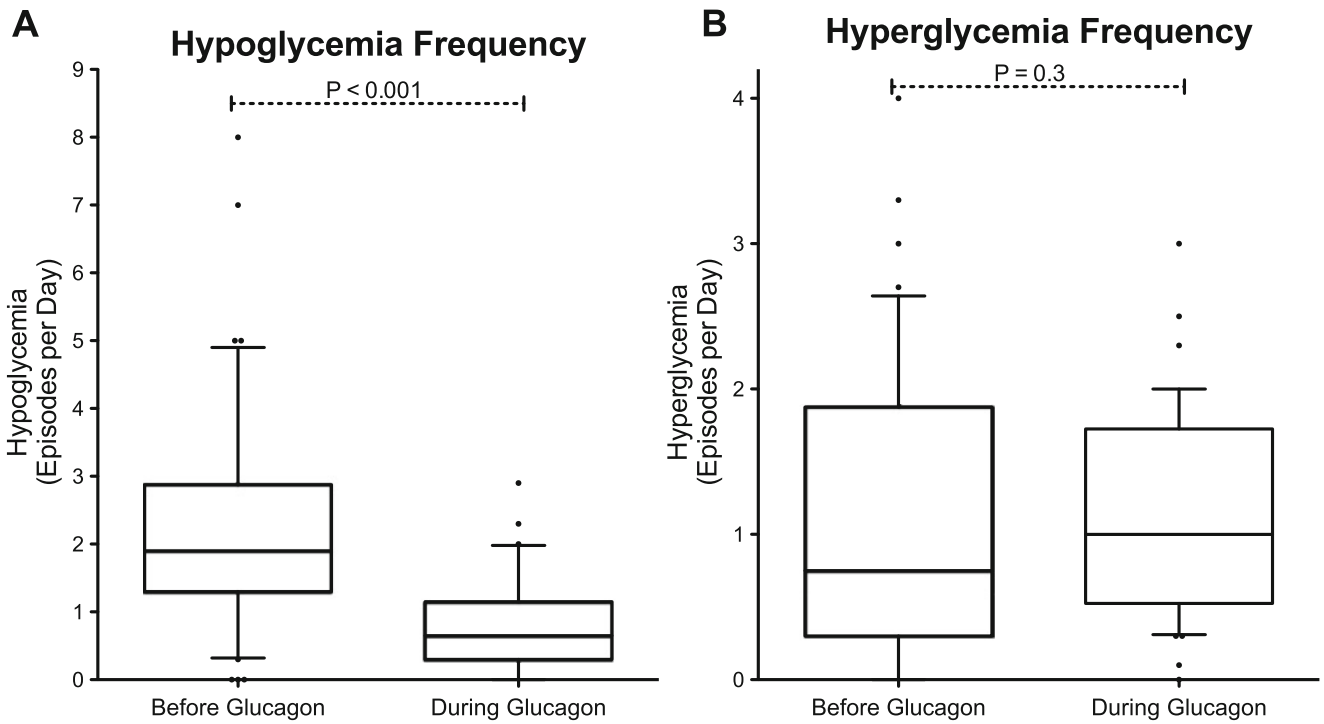

Fig. 2 Frequency of (**a**) hypoglycemia episodes (plasma glucose <70 mg/dL) and (**b**) hyperglycemia episodes (plasma glucose >140 mg/dL) per day in children with congenital hyperinsulinism up to 4 days prior to and 4 days after starting continuous glucagon infusion. Data presented as median (range)

The large number of infants included in this study provides an opportunity to describe the effect of glucagon administration in this patient population and to observe the safety of this treatment. This study is limited by its retrospective design and absence of a control group for comparison. However, by describing only infants who were scheduled for surgical management of their HI, only infants with severe disease and high risk of hypoglycemia were included. Although it is conceivable that GIR prior to starting glucagon may have been unnecessarily high due to insufficient weaning of intravenous glucose, this is unlikely. The frequency of episodes of hypoglycemic was higher prior to starting glucagon, suggesting that it was not possible to wean the GIR further prior to glucagon treatment.

In conclusion, this study demonstrates that continuous glucagon infusion is an effective treatment in severe congenital HI. Starting a glucagon infusion allows for a reduction in GIR in most infants, which will facilitate a reduction in intravenous volume and/or glucose concentration administered. Furthermore, we have not demonstrated significant safety concerns in using glucagon but recommend close observation as these infants are at risk of complications due to their underlying disease, high fluid requirements, and coexisting medications.

Funding Sources

This study was supported by training grant T32DK063688-13S to J.J.L. and grant 5R01DK098517 to D.D.D.L.

Compliance with Ethics Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

Conflict of Interest

Colin Hawkes, Juan Lado, Stephanie Givler, and Diva D. De Leon declare that they have no conflict of interest.

Author Contributions

Colin Hawkes analyzed data and wrote the manuscript, Juan Lado collected and analyzed data and wrote the manuscript, Stephanie Givler collected data, and Diva D. De Leon designed study and edited the manuscript.

References

Barrington KJ (2000) Umbilical artery catheters in the newborn: effects of position of the catheter tip. Cochrane Database Syst Rev. CD000505

Belik J, Musey J, Trussell RA (2001) Continuous infusion of glucagon induces severe hyponatremia and thrombocytopenia in a premature neonate. Pediatrics 107:595–597

Carter PE, Lloyd DJ, Duffty P (1988) Glucagon for hypoglycaemia in infants small for gestational age. Arch Dis Child 63:1264–1266

Charsha DS, McKinley PS, Whitfield JM (2003) Glucagon infusion for treatment of hypoglycemia: efficacy and safety in sick, preterm infants. Pediatrics 111:220–221

Ferrara C, Patel P, Becker S, Stanley CA, Kelly A (2016) Biomarkers of insulin for the diagnosis of hyperinsulinemic hypoglycemia in infants and children. J Pediatr 168:212–219

Food and Drug Administration (n.d.) Glucagon for injection (rDNA origin). https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/201849s002lbl.pdf

Hawkes CP, Adzick NS, Palladino AA, De Leon DD (2016) Late presentation of fulminant necrotizing enterocolitis in a child with hyperinsulinism on octreotide therapy. Horm Res Paediatr 86 (2):131–136

Hussain K, Bryan J, Christesen HT, Brusgaard K, Aguilar-Bryan L (2005) Serum glucagon counterregulatory hormonal response to hypoglycemia is blunted in congenital hyperinsulinism. Diabetes 54:2946–2951

Lord K, De Leon DD (2013) Monogenic hyperinsulinemic hypoglycemia: current insights into the pathogenesis and management. Int J Pediatr Endocrinol 2013:3

Lord K, Dzata E, Snider KE, Gallagher PR, De Leon DD (2013) Clinical presentation and management of children with diffuse and focal hyperinsulinism: a review of 223 cases. J Clin Endocrinol Metab 98:E1786–E1789

Lord K, Radcliffe J, Gallagher PR, Adzick NS, Stanley CA, De Leon DD (2015) High risk of diabetes and neurobehavioral deficits in individuals with surgically treated hyperinsulinism. J Clin Endocrinol Metab 100(11):4133–4139

Meissner T, Wendel U, Burgard P, Schaetzle S, Mayatepek E (2003) Long-term follow-up of 114 patients with congenital hyperinsulinism. Eur J Endocrinol 149:43–51

Miralles RE, Lodha A, Perlman M, Moore AM (2002) Experience with intravenous glucagon infusions as a treatment for resistant neonatal hypoglycemia. Arch Pediatr Adolesc Med 156:999–1004

Palladino AA, Stanley CA (2011) A specialized team approach to diagnosis and medical versus surgical treatment of infants with congenital hyperinsulinism. Semin Pediatr Surg 20:32–37

Quesada I, Tuduri E, Ripoll C, Nadal A (2008) Physiology of the pancreatic alpha-cell and glucagon secretion: role in glucose homeostasis and diabetes. J Endocrinol 199:5–19

Steinkrauss L, Lipman TH, Hendell CD, Gerdes M, Thornton PS, Stanley CA (2005) Effects of hypoglycemia on developmental outcome in children with congenital hyperinsulinism. J Pediatr Nurs 20:109–118

Unger RH, Cherrington AD (2012) Glucagonocentric restructuring of diabetes: a pathophysiologic and therapeutic makeover. J Clin Invest 122:4–12

Vajravelu ME, De Leon DD (2018) Genetic characteristics of patients with congenital hyperinsulinism. Curr Opin Pediatr 30 (4):568–575