Experience With Intravenous Glucagon Infusions as a Treatment for Resistant Neonatal Hypoglycemia

Robin E. Miralles, MB, BCh, MRCPCH; Abhay Lodha, MD, DM; Max Perlman, MB, FRCPC; Aideen M. Moore, MD, FRCPC

Background: Based on limited anecdotal evidence, glucagon is used for the management of intractable neonatal hypoglycemia persisting in the face of high glucose administration rates.

Objective: To evaluate the short-term response of blood glucose levels to an intravenous infusion of glucagon.

Design: A retrospective observational study in which all newborns who received glucagon infusions (usual dose, 0.5-1 mg/d) during a 5-year period were identified (N=55). The common causes of hypoglycemia were perinatal stress, intrauterine growth restriction, prematurity, and maternal diabetes mellitus. Laboratory blood glucose measurements made between 24 hours before and 72 hours after the start of the glucagon infusion and the rates of glucose administration during the same period were analyzed. The effects of glucagon on sodium and platelet levels were also examined.

Setting: University referral hospital.

Results: A statistically and clinically significant rise in blood glucose concentration, from a mean of 36.3 to 93.0 mg/dL (2.02-5.17 mmol/L), was observed within 4 hours of starting glucagon administration. The change was unrelated to the cause of the hypoglycemia. The frequency of hypoglycemic episodes was significantly reduced, and no further episodes of severe hypoglycemia (glucose level, <20 mg/dL [<1.1 mmol/L]) occurred. Five patients, 4 of whom were preterm newborns with intrauterine growth restriction, required additional glycemic treatment. Seventy-five percent of newborns were thrombocytopenic before starting glucagon infusion, and in 9 newborns platelet counts decreased following glucagon infusion. There was no hyponatremia attributable to glucagon.

Conclusion: Glucagon infusions appear to be beneficial for problematic neonatal hypoglycemia of different causes.

Arch Pediatr Adolesc Med. 2002;156:999-1004

Gluconeogenesis is the primary fuel used by the brain and is essential for cerebral metabolism. At birth, the healthy newborn adapts to an environment that provides an intermittent supply of glucose. Glycogenolysis and gluconeogenesis are therefore needed to maintain blood glucose levels.1 Insulin secretion, high in the fetus, is suppressed following delivery by an adrenergic mechanism, and glucagon secretion is stimulated.2 Endogenous glucagon is thought to play a primary role in inducing hepatic gluconeogenesis; under normal circumstances, levels of glucagon rise rapidly when the umbilical cord is clamped. An impaired endogenous rise in pancreatic glucagon has been reported in infants of diabetic mothers.3 Factors such as asphyxia, intrauterine growth restriction, prematurity, or sepsis may disturb the metabolic transition to postnatal life so that the release of blood glucose from the liver is insufficient to meet the newborn’s utilization rate.4 When hypoglycemia is severe (glucose level, 0-18 mg/dL [0-1 mmol/L]) and prolonged, permanent brain injury or death is likely to occur.57 However, less severe hypoglycemia (glucose level, <47 mg/dL [<2.6 mmol/L]), even in asymptomatic newborns, may lead to neural dysfunction and subsequent permanent neurologic impairment.8-10 Consensus is lacking on the definition of normoglycemia and hypoglycemia in neonates, although many authorities recommend intervention if blood glucose levels fall below 47 mg/dL (2.6 mmol/L).9,11 A recent consensus statement suggested that intervention should be considered for newborns with symptoms suggestive of hypoglycemia with blood glucose levels below 45 mg/dL (2.5 mmol/L).12

In most cases, neonatal hypoglycemia responds to early feeding or intrave-
ous (IV) dextrose infusion given at an adequate rate. In a few newborns, this first-line treatment is not sufficient, and hormonal treatment with either glucagon or glucocorticoids may be started. The effect of bolus doses of glucagon has been studied. Glucagon has been in use in our neonatal intensive care unit (NICU) for more than 20 years, but there is little information available on the use of IV glucagon infusions in the management of neonatal hypoglycemia. Other authorities recommend hydrocortisone before giving glucagon. Because there is no consensus as to which approach is most efficacious, there is a need for evaluation of the different treatments for refractory hypoglycemia. Therefore, we summarized our recent experience with IV glucagon infusions in the treatment of resistant neonatal hypoglycemia, including an evaluation of recently reported adverse effects.

**PARTICIPANTS AND METHODS**

**STUDY PARTICIPANTS**

Our NICU is the outborn referral center (ie, the referral center for those born outside that unit) for severely ill newborns from a defined geographic area with approximately 65,000 annual births. We identified all patients admitted to our NICU who received a glucagon infusion for hypoglycemia during a 5-year period (1994-1998) and who had at least one laboratory-determined blood glucose level both before and after commencing the glucagon infusion (N=55, 37 male and 18 female newborns). Data on growth parameters, gestational age, causes of hypoglycemia, age of glucagon administration, and initial dosage and duration of treatment were collected. Prematurity was defined as a gestational age less than 37 completed weeks. The designation of perinatal stress was based on both intrauterine growth restriction (including fetal heart rate monitoring, cord blood pH) and postnatal clinical evidence of encephalopathy (persisting after correction of hypoglycemia), including radiologic evidence of brain abnormality. The definition of intrauterine growth restriction (IUGR) was based on a birth weight less than the 10th centile. Approval for this study was obtained from the hospital institutional review board.

**BLOOD GLUCOSE MEASUREMENTS**

Only laboratory-determined plasma glucose levels were recorded in this study because of inaccuracy of bedside measures. For this study, hypoglycemia was defined as a blood glucose level less than 47 mg/dL (2.6 mmol/L). Data were collected on blood glucose levels from 24 hours before glucagon administration to 72 hours after (24, 16-8, 4-0 hours before glucagon use and 0-4, 4-8, 8-16, 24, 48, and 72 hours after the start of the infusion). Recognizing that blood glucose values are a continuum, the severity of hypoglycemia was stratified into 3 groups: less than 47 mg/dL (2.6 mmol/L), less than 36 mg/dL (2.0 mmol/L), and less than 20 mg/dL (1.1 mmol/L). Categorization was thought to be important for 2 reasons. First, there is no agreement as to what constitutes a significant level of hypoglycemia, although it is agreed that the lower the glucose level, the more likely it is to be significant. Second, the effect of glucagon on the varying degrees of hypoglycemia could be observed.

The number of episodes of hypoglycemia and the number of days on which hypoglycemia occurred were documented. Information was obtained on the timing of these episodes and whether they occurred before, during, or after the glucagon infusion. Episodes of hypoglycemia occurring at the referring hospitals were included. Generally, repeated laboratory glucose levels were obtained at the NICU until stable normoglycemia was achieved. Because the number of episodes of hypoglycemia detected would depend to some extent on the frequency with which blood glucose levels were checked, the results were also expressed as the number of days on which hypoglycemia was detected and the number of patients who had hypoglycemic episodes.

For most patients (n=49), 1 mg of glucagon was infused over 24 hours (average dose, 10-20 µg/kg hourly) regardless of gestational age or birth weight. At the time glucagon was initiated, rates of glucose infusion were mostly between 6 and 12 mg/kg per minute. Once blood glucose levels were stable on average glucose requirements, glucagon was weaned by decreasing infusion rates over 24 to 72 hours.

The infusion rates of dextrose-containing solutions and the amounts of enteral feed at each time point (24, 12, and 6 hours before glucagon administration and 0, 6, 12, 24, 48, and 72 hours after the glucagon infusion was started) were recorded. The composition of any expressed breast milk was assumed to approximate that previously quoted. Daily weights were recorded to calculate the administration rates of glucagon and glucose.

Serum sodium values and platelet counts were examined during the 5-year study period, 55 newborns were observed from 48 hours before glucagon administration to 72 hours after the start of the infusion. In a limited number of patients, additional biochemical data obtained during hypoglycemia included the presence of ketonuria and “critical blood work” information (insulin, β-hydroxybutyrate, and free fatty acid concentrations).

**RESULTS**

**STUDY POPULATION**

During the 5-year study period, 55 newborns were observed to have received glucagon infusions. Gestational ages ranged from 24 weeks to 41 weeks (mean and median, 36 weeks) and birth weights from 0.46 to 5.2 kg (mean±SD, 2.35±0.99 kg). Hypoglycemia was attributed to more than a single cause in 29 patients, whereas in 2 cases the cause was undetermined (Figure 1). The largest subgroups were perinatal stress alone and in combination (n=26) and IUGR alone and in combination (n=25). In 39 patients there was evidence of fetal distress, leading to emergency cesarean delivery in 38. The overall cesarean delivery rate was 69%. Reduced or absent fetal movements were reported in 14 patients (25%). Seizures were observed in 10 neonates, and phenobarbital was given in addition to glucose and glucagon. In 4 cases, the seizures were temporally associated with hy-
poglycemia. Body mass indexes (calculated as weight in kilograms divided by the square of height in meters) were available in 16 of the patients with IUGR. These ranged from 7.4 to 11.8, with a median of 9.0 (mean, 9.4±1.4). The mean±SD age of patients when they started glucagon infusion was 4.5±7.1 days. In 32 newborns (58%), episodes of hypoglycemia had been occurring for more than 24 hours before the administration of glucagon.

**INITIAL RESPONSE TO GLUCAGON**

The initial response to glucagon was assessed by calculating the difference between the last preglucagon blood glucose level and the first blood glucose level after starting the infusion. A statistically and clinically significant rise in blood glucose concentration, from a mean of 38.9 to 110 mg/dL (2.16-6.11 mmol/L), was observed within 1 hour of starting glucagon infusion. The median rise in glucose concentration was 45 mg/dL (2.5 mmol/L) (P<.001) (Figure 2). There was no significant increase in glucose administration to account for this rise in blood glucose level. The mean glucose delivery rate was 8.8 mg/kg per minute 6 hours before and 9.4 mg/kg per minute 6 hours after the addition of glucagon. Only 1 patient, a severely growth-restricted, 26-week gestation newborn (480-g birth weight), did not show an early rise in glucose concentration. This newborn subsequently showed a rise in blood glucose level to 48.6 mg/dL (2.7 mmol/L) at 8 hours after glucagon infusion.

There was no correlation seen in our data between the glucagon dose per kilogram (range, 6-95 µg/kg hourly) and the initial rise in glucose levels. In addition, there was no significant difference in the rise in glucose produced by glucagon infusion rates less than 20 µg/kg hourly (n=32) and those greater than 20 µg/kg hourly (n=23) (Mann-Whitney U test, P=.63).

**GLUCOSE ADMINISTRATION**

There were no statistically significant differences in glucose administration during the study period. Glucose infusions ranged from medians of 9.27 mg/kg per minute at the start of glucagon infusion to 9.16 mg/kg per minute 48 hours later.

ASSOCIATION BETWEEN GLUCAGON INFUSION AND HYPOGLYCEMIC EPISODES

No patient had severe hypoglycemia (glucose level, <20 mg/dL [<1.1 mmol/L]) after the glucagon infusions were started. The relative risk (RR) of a patient having a blood glucose level less than 47 mg/dL (2.6 mmol/L) during the glucagon infusion compared with the period before glucagon administration was 0.47 (95% confidence interval [CI], 0.36-0.62). For blood glucose levels less than 36 mg/dL (2.0 mmol/L), the corresponding RR was 0.32 (95% CI, 0.21-0.48) on any day (Figure 3). The RRs for the number of days on which blood glucose concentrations were less than 47 and 36 mg/dL (2.6 and 2.0 mmol/L) were 0.40 (95% CI, 0.32-0.51) and 0.21 (95% CI, 0.13-0.31), respectively (Figure 3).
In 29 patients there was more than one cause of hypoglycemia so that the subgroups analyzed included combinations of causes and single causes alone. The association between the blood glucose concentration and glucagon infusion for the various diagnostic groups is shown in the Table. The initial rise in glucose ranged from a mean of 44.5 mg/dL (2.47 mmol/L) for the preterm newborn group to 65.2 mg/dL (3.62 mmol/L) in the perinatal stress group. There were no statistically significant between-group differences. However, the maximum increase was smaller in the preterm group (79 mg/dL [4.4 mmol/L]) compared with the other subgroups (144-173 mg/dL [8-9.6 mmol/L]). The mean increase in the 4 newborns weighing less than 1 kg was 22.1 mg/dL (1.23 mmol/L), with a range of −5.4 to 46.8 mg/dL (−0.3 to 1.23 mmol/L). All 4 patients subsequently died of causes other than hypoglycemia (necrotizing enterocolitis with sepsis in 2 newborns, overwhelming sepsis in 1, and pulmonary hypoplasia and asphyxia in 1). The median age of the start of glucagon administration was 26 days compared with a median age of 2 days for the study group as a whole. Among the subgroups, the infants of diabetic mothers group showed the largest reduction in the occurrence of hypoglycemia (Figure 3).

The change in blood glucose concentration in patients who were receiving enteral or IV lipids (n = 12) at the time that the glucagon administration was started compared with the change in glucose in the patients not receiving lipids (n = 43) was not significant (P = 0.62).

OTHER INVESTIGATIONS AND TREATMENTS

Insulin levels were measured in 12 cases, and β-hydroxybutyrate and free fatty acid levels in 13 patients. In 2 patients, the insulin level was unrecordable (appropriate during hypoglycemia). In the remaining 10 patients, the range of insulin was 3.5 to 23.1 µU/mL (25-166 pmol/L). The 2 patients with undetectable insulin responded to glucagon with a mean rise in blood glucose level of 69 mg/dL (3.85 mmol/L). In no case was ketonuria detected during hypoglycemia (n = 12).

CHANGES IN SERUM SODIUM

Serum sodium values for 48 hours before to 72 hours after glucagon administration were available for 38 newborns. Serum sodium was unchanged following glucagon infusion in 21 newborns, was initially normal then decreased while taking glucagon in 7, and was initially low and became normal while taking glucagon in 10.

CHANGES IN PLATELET COUNTS

Of 45 newborns who had platelet counts measured before the glucagon infusion, 9 (25%) had normal values (>150 × 10^3/µL) and 20 had counts less than 100 × 10^3/µL. Platelet counts for 48 hours before to 72 hours after glucagon use were available for 36 newborns. The platelet count was unchanged after glucagon administration in 26 newborns (variation of <1 SD), the count increased in 1, and it decreased in 9. Of the 9, 2 had major venous thromboses, and 1 had group B streptococcal sepsis concomitant with the initiation of glucagon. Of the remaining 6 cases, 4 were infants of diabetic mothers.

RECURRENCE OF HYPOGLYCEMIA AND THE ADMINISTRATION OF OTHER GLYCEMIC TREATMENTS

In 11 patients (20%), glucagon administration was re-started after it was discontinued, within 24 hours in 6 of the 11. Of the 29 newborns who had no episodes of hypoglycemia during the glucagon infusion, 4 had episodes of hypoglycemia (glucose level, 36 mg/dL [<2.0 mmol/L]) after glucagon use was discontinued. Five patients (9%) were treated with other glycemic medications. Three newborns received diazoxide (all 3 were preterm and had IUGR, and 1 proved to have undetectable insulin), 1 was given dexamethasone (preterm and IUGR), and 1 received hydrocortisone (perinatal stress).

This study demonstrates a striking association between glucagon infusion and rising blood glucose levels (median rise of 45 mg/dL [2.5 mmol/L] within 4 hours of initiating the infusion) and a significant reduction in the
Management of hypoglycemia is an important problem in all newborn nurseries. Most cases of neonatal hypoglycemia respond to early feeding or intravenous dextrose administration, but in some severe cases, hormonal treatment with either glucagon or glucocorticoids is required. There is no consensus regarding which approach is the most effective. Despite limited evidence, glucagon is widely used for the management of persistent neonatal hypoglycemia. This retrospective study, to our knowledge the first from North America, shows that intravenous glucagon infusions significantly increased blood glucose concentrations in neonatal hypoglycemia. Glucagon was also able to prevent further episodes of severe hypoglycemia and was effective in a wide variety of conditions, including hypoglycemia associated with asphyxia, intrauterine growth restriction, prematurity, and infants of diabetic mothers.

What This Study Adds

Management of hypoglycemia is an important problem in all newborn nurseries. Most cases of neonatal hypoglycemia respond to early feeding or intravenous dextrose administration, but in some severe cases, hormonal treatment with either glucagon or glucocorticoids is required. There is no consensus regarding which approach is the most effective. Despite limited evidence, glucagon is widely used for the management of persistent neonatal hypoglycemia. This retrospective study, to our knowledge the first from North America, shows that intravenous glucagon infusions significantly increased blood glucose concentrations in neonatal hypoglycemia. Glucagon was also able to prevent further episodes of severe hypoglycemia and was effective in a wide variety of conditions, including hypoglycemia associated with asphyxia, intrauterine growth restriction, prematurity, and infants of diabetic mothers.
paring glucagon to steroids or the effect of glucagon infusions in different doses may be good starting points.

Accepted for publication May 9, 2002.

Corresponding author and reprints: Aideen M. Moore, MD, FRCPC, Division of Neonatology, Hospital for Sick Children and University of Toronto, 555 University Ave, Toronto, Ontario, Canada M5G 1X8 (e-mail: aideen.moore@sickkids.ca).

REFERENCES


