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Original Article

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Metabolic acidosis during continuous glucagon therapy for neonatal hypoglycemia

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ABSTRACT

Objectives: Refractory neonatal hypoglycemia may be treated with glucagon infusions, which have been associated with thrombocytopenia and hyponatremia. After anecdotally noting metabolic acidosis during glucagon therapy in our hospital, an outcome not previously reported in the literature, we aimed to quantify occurrence of metabolic acidosis (base excess >−6) as well as thrombocytopenia and hyponatremia during treatment with glucagon.

Methods: We performed a single-centre retrospective case series. Descriptive statistics were used and subgroups compared with Chi-Square, Fisher's Exact Test, and Mann–Whitney U testing.

Results: Sixty-two infants (mean birth gestational age 37.2 weeks, 64.5% male) were treated with continuous glucagon infusions for median 10 days during the study period. 41.2% were preterm, 21.0% were small for gestational age, and 30.6% were infants of diabetic mothers. Metabolic acidosis was seen in 59.6% and was more common in infants who were not born to diabetic mothers (75% versus 24% in infants of diabetic mothers, P<0.001). Infants with versus without metabolic acidosis had lower birth weights (median 2,743 g versus 3,854 g, P<0.01) and were treated with higher doses of glucagon (0.02 versus 0.01 mg/kg/h, P<0.01) for a longer duration (12.4 versus 5.9 days, P<0.01). Thrombocytopenia was diagnosed in 51.9% of patients.

Conclusions: In addition to thrombocytopenia, metabolic acidosis of unclear etiology appears to be very common with glucagon infusions for neonatal hypoglycemia, especially in lower birth weight infants or those born to mothers without diabetes. Further research is needed to elucidate causation and potential mechanisms.

Keywords: Acidosis; Glucagon; Hypoglycemia; Infant/newborn.

Neonatal hypoglycemia is one of the most common diagnoses requiring intervention and admission to neonatal intensive care units (NICUs) in Canada and other developed settings (1,2). Risk factors include prematurity, small for gestational age (SGA)/intrauterine growth restriction or large for gestational age (LGA), and infants of diabetic mothers (IDMs) (1). A common etiology is hyperinsulinemia, which although usually transient, can require treatment for weeks to prevent long-term sequelae associated with hypoglycemia, such as impaired executive function (1–3).

In infants with hypoglycemia, especially with hyperinsulinemic hypoglycemia (HIH), such as IDMs, normalization, and maintenance of glucose may be challenging with dextrose-containing solutions alone. Intravenous fluids may be limited by type of access, as concentrated dextrose requires central lines, as well as the ability of the neonate to tolerate high volumes of fluids without dilutional hyponatremia (2,4). In refractory neonatal hypoglycemia, intravenous glucagon, which stimulates hepatic gluconeogenesis and glycogenolysis and inhibits glycogenesis, may be used off-label (3,5–7). Although neonatal use has been

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reported throughout the world (3–6), there is a paucity of literature on safety data, with a few reports of potential hyponatremia or thrombocytopenia (7,8).

In concordance with national guidelines (2), continuous glucagon infusions are prescribed in the NICU at the Hospital for Sick Children, a quaternary referral NICU in Toronto, Canada, to aid with glucose management for persistent and refractory hypoglycemia. As this medication has become frequent in our NICU, potentially due to increasing frequency of gestational diabetes and therefore IDMs (9), we noted a high frequency of concomitant metabolic acidosis. However, to our knowledge, there are no reports in the literature of metabolic acidosis associated with glucagon infusions. Acidosis itself can be harmful, but can also result in unintended consequences, as infants may be investigated for inborn errors of metabolism.

Therefore, the aim of this study was to determine incidence of biochemical abnormalities in infants treated with continuous glucagon, especially metabolic acidosis, assessing for potential differences in the various neonatal populations affected by refractory hypoglycemia.

METHODS

This was a single referral centre retrospective case series. We utilized a convenience sample of infants admitted to our NICU from June 2018 (when our electronic medical record [EMR] changed to our current system, Epic (Version date 05/2021; Verona, Wisconsin)) through December 2020. Inpatient drug use evaluation reports from the EMR were searched for patients who received a glucagon infusion for at least 1 hour. Our practice is to utilize continuous intravenous glucagon infusions for hypoglycemia refractory to increases in glucose infusion rates (GIR) ≥12 mg/kg/min, especially in the immediate newborn period to prevent supraphysiologic intravenous fluid volumes (over 100 mL/kg/day in term newborns), or potentially at lower GIRs if there is a lack of central access to give concentrated (>12.5%) dextrose-containing iv fluids. Of note, our practice includes routine use of acetate in intravenous fluids to compensate for metabolic acidosis. The study was approved by research ethics board (REB) (#1000073727) with waiver of consent.

The EMR was utilized to obtain background variables (birth weight, birth gestational age, birth weight percentage on growth charts (WHO for term ≥37 weeks, Fenton for preterm <37 weeks at birth) to categorize small (SGA; <10th %), appropriate (AGA; 10th % to 90th %), or LGA (>90th %) (10,11), other common diagnoses potentially related to hypoglycemia (IDM, hypoxic ischemic encephalopathy [HIE]), glucagon prescription [starting and maximum dose, duration of therapy], and insulin obtained as part of a 'critical lab' panel (including cortisol, ketones, growth hormone, etc.), obtained when point of care glucose (confirmed by serum) is <2.7 mmol/L. Outcome variables included glucose, blood gas (capillary, venous, or arterial) values (pH, bicarbonate, base deficit), sodium, ketones (urine or serum ('negative' considered [<0.3 mmol/L by laboratory)], serum amino acids, and platelet counts—values were collected if available at initiation of glucagon as well as longitudinally during glucagon therapy. If labs were drawn multiple times, the 'worst' (i.e., greatest base excess, lowest platelet count) result was reported. Metabolic acidosis was defined by base excess greater than −6 (12,13), hyponatremia by sodium <130 mmol/L (13), and thrombocytopenia by platelet count $<100 \times 10^9$/L. Subjects were given a study identification number, and data stored in a deidentified manner in accordance with REB recommendations. Total NICU admissions, as well as admissions utilizing ICD-9 codes for thrombocytopenia, hypoglycemia, and metabolic acidosis were pulled from the EMR.

Descriptive characteristics utilized mean with 95% confidence interval if normally distributed or median (interquartile range) if not. Subgroups (sex, preterm [<37 weeks] versus term gestation at birth, birthweight status [SGA, AGA, and LGA as well as dichotomized to SGA versus not], IDM versus not, and HIE versus not) were analyzed to assess for any associations with potential glucagon side effects: metabolic acidosis, thrombocytopenia, and hyponatremia. Groups were compared with two-sided Chi-square or Fisher's exact test (for small sample sizes if expected cell count <5); Mann–Whitney testing was used for continuous variables. Statistical analysis was performed using SPSS version 26 (IBM, Armonk, NY, USA).

RESULTS

A search revealed 64 potential patients prescribed glucagon out of 3,504 NICU admissions. After obtaining patient details, 62 patients were included (Figure 1: Study Cohort). Subject characteristics are summarized in Table 1. Lab results and glucagon dosing are shown in Table 2; not all subjects had all labs drawn. Insulin was often elevated, signaling HIH as the commonest diagnosis. Glucagon therapy had a wide-ranging duration, from less than 1 day to 58 days. Metabolic acidosis and thrombocytopenia were common in this quaternary NICU population. Of

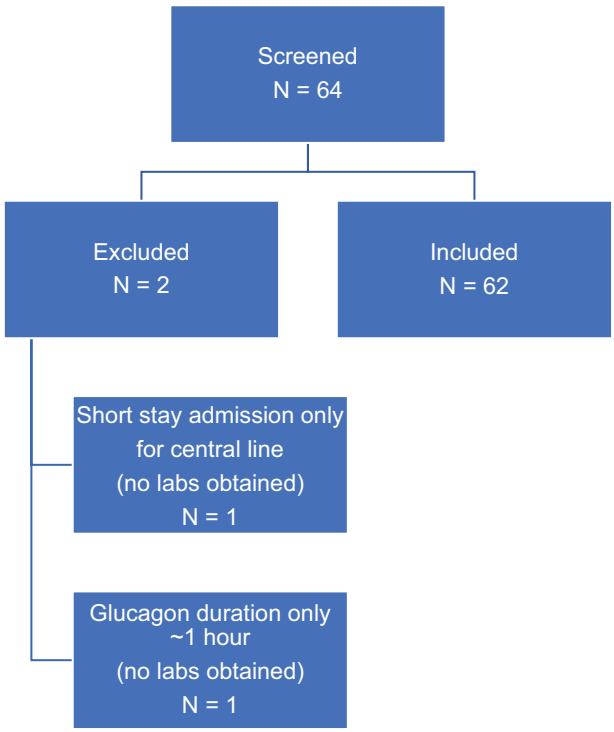

Figure 1. Study cohort.

Table 1. Subject characteristics

N=62		n (%) or mean (95% CI) or median [IQR] if non-normal
Male sex		40 (64.5%)
Gestational age (weeks)		37.2 (36.6-37.8)
Preterm (<37 weeks gestational age at birth)		26 (41.9%)
Birthweight (g)		3,212 (2,952–3,471)
Birth weight growth chart percentile		68.1 [12.9, 94.9]
Birth Weight Category	Small for GA (<10th%)	13 (21.0%)
	Appropriate for GA (10th–90th%)	27 (43.5%)
	Large for GA (>90th%)	22 (35.5%)
Diagnosis	IDM only	14 (22.6%)
	HIE + IDM	5 (8.1%)
	HIE only	8 (12.9%)
	Hypoglycemia NOS	35 (56.5%)

CI Confidence interval; GA Gestational age; HIE Hypoxic ischemic encephalopathy; IDM Infant of diabetic mother; IQR Interquartile range; NOS Not otherwise specified.

3,504 admissions, which included our cohort, 236 (6.7%) had hypoglycemia and 386 (11.5%) thrombocytopenia as an ICD-9 diagnostic code; metabolic acidosis was not listed in any patient. Nearly 18% of the 62 patients had a metabolic workup. In cases of metabolic acidosis, there was typically respiratory compensation that negated need for treatment, with only 3/62 patients with metabolic acidosis having lowest recorded pH≤7.20; of note, none of these 3 had HIE.

To assess potential associations with duration or dose of glucagon, we dichotomized subjects into metabolic acidosis versus not. Those with (n=34) versus without (n=23) acidosis were given higher maximum doses of glucagon (median 0.02 [IQR 0.02, 0.03] versus 0.01 [IQR 0.01, 0.02] mg/kg/h, Mann–Whitney P<0.01) for a longer duration (median 12.4 [8.2, 21.7] versus 5.9 [0.8, 12.3] days, P<0.01) than those without acidosis. Of note, 34 infants (21 with metabolic acidosis) had serum ketones (25 patients), urine ketones (1 patient) or both (8 patients) checked with 'critical labs' for hypoglycemia, some multiple times, for 56 samples. All were negative for ketones. Thirteen samples were taken before initiation of glucagon. Eighteen patients with acidosis had ketones checked on glucagon.

Table 3 focuses on the two common outcomes of metabolic acidosis and thrombocytopenia in subgroup analyses. Acidosis was less common in LGA infants, although not statistically significant with categorical variables. However, when birthweight was assessed as a continuous variable, infants with metabolic acidosis had lower birthweights, median 2,743 g (IQR 2,263 g, 3,575 g) versus 3,854 g (IQR 2,640 g, 4,503 g) in those without acidosis, P<0.01. Infants with metabolic acidosis trended toward lower birth weight percentiles (median 47.7%, [9.9%, 91.1%] versus 90.0% [38.2%, 99.1]) without acidosis, P=0.07). Acidosis was also more frequent in non-IDM infants and borderline more frequent (P=0.05) in infants without HIE. Thrombocytopenia increased with decreasing birthweight category, seen most commonly in the SGA group. There was overlap with metabolic acidosis and thrombocytopenia, with 18/28 infants with thrombocytopenia having both diagnoses; 6 (33%) of these 18 infants were SGA. No associations were noted with metabolic acidosis nor thrombocytopenia with infant sex (data not shown).

A subgroup analysis utilizing the above groups (birthweight status, IDM, etc.) was also run to assess hyponatremia. No statistically significant associations were seen for hyponatremia, which was a relatively rare diagnosis (16.3% of cohort).

DISCUSSION

In this retrospective case series at a quaternary referral NICU of infants treated with glucagon for refractory hypoglycemia, metabolic acidosis was very common, seen in nearly 60% of patients. Unlike thrombocytopenia, which was also common, metabolic acidosis with glucagon infusions, to our knowledge, has not been previously reported. Although it could be postulated that infants at a quaternary NICU may have other reasons to have metabolic acidosis, our results suggest that longer duration and higher dose of glucagon infusions were more likely to be associated with acidosis, although this could be confounded by sicker infants who were more hypoglycemic. It is challenging to know what an incidence of metabolic acidosis 'should' be in the NICU, as literature is limited. Schanler described a cohort of stable infants on fortified human milk feeds born at <32 weeks and reported a 5% incidence (14). In another extreme, Bourchier described a cohort of extremely low birth weight infants, many on pressors, in which 97% had metabolic acidosis (12). Our study population, with a mean gestational age of 37 weeks at birth, is dissimilar to these very preterm populations, so it is unclear what incidence one would expect, and what a 'control group' would be—hypoglycemic infants not on glucagon likely have milder hypoglycemia, and infants without hypoglycemia admitted to our quaternary NICU have diagnoses like sepsis where metabolic acidosis is common. We attempted to utilize ICD-9 codes to compare our cohort to others in our NICU, but no infants were assigned a diagnostic code for metabolic acidosis, likely as it was more of an endpoint than a 'diagnosis'. However, due to presumably unexplained acidosis, 18% of the cohort had a workup performed to assess for rare inborn errors of metabolism, reflecting that clinicians thought the acidosis unusual or out of keeping with clinical presentation.

Table 2. Lab results and glucagon dosing

N=62	N (%) or mean (95% CI) or median [IQR] if non-normal
Initial glucose (mmol/L)	1.6 [0.8, 2.7]
Glucose (mmol/L) for 'critical labs*' (first set sent) (n=45)	2.7 [2.1, 3.4]
Lowest glucose (mmol/L) on glucagon (n=54)	4.8 [4.1, 5.9]
Insulin (pmol/L) for 'critical labs*' (first set sent) (n=34)	81.0 [34.5, 163.5]
Initial glucagon dose (mg/kg/h)	0.010 [0.010, 0.019]
Maximum glucagon dose (mg/kg/h)	0.020 [0.010, 0.201], maximum 0.100
Glucagon duration (days)	10.1 [4.8, 16.8], maximum 58.1
Lowest pH (n=57)	7.31 [7.26, 7.34], minimum 6.98
Lowest base excess (mmol/L) (n=57)	−8.0 [−10.0, −5.0], maximum -23
Lowest bicarbonate (mmol/L) (n=57)	18.5 (17.5–19.5), minimum 8
Metabolic acidosis (base excess over −6) (n=57)	34 (59.6%)
Had metabolic workup performed due to metabolic acidosis (serum amino acids sent)	11 (17.7%)
Lowest Sodium (mmol/L) (n=49)	135 (133–137), minimum 123
Hyponatremia (Sodium <130 mmol/L) (n=49)	8 (16.3%)
Thrombocytopenia (platelets <100) (n=54)	28 (51.9%)

* 'critical labs' panel sent if glucose <2.7 mmol/L.
Note 'n' for each lab result may not equal total N of 62 as not all labs available for all patients.

Table 3. Subgroup outcomes

		Metabolic acidosis (lowest base excess greater than −6) (n=57)	P value (Chi square [C] or Fisher's exact test [F])	Thrombocytopenia (lowest platelets <100) (n=54)	P value (Chi square [C] or Fisher's exact test [F])
Birth gestation	Preterm (<37 weeks)	18/25 (72%)	0.09 (C)	15/24 (63%)	0.16 (C)
	Term	16/32 (50%)		13/30 (43%)	
Birth Weight Category	SGA	8/12 (67%)	0.14 (C)	8/11 (73%)	0.02 (C)
	AGA	17/24 (71%)		15/24 (63%)	
	LGA	9/21 (43%)		5/19 (26%)	
IDM	Yes	4/17 (24%)	<0.001 (C)	5/14 (36%)	0.16 (C)
	No	30/40 (75%)		23/40 (58%)	
HIE	Yes	4/12 (33%)	0.05 (F)	9/11 (82%)	0.04 (F)
	No	30/45 (67%)		19/43 (44%)	

AGA Appropriate for gestational age (GA); HIE Hypoxic ischemic encephalopathy; IDM Infant of a diabetic mother; LGA Large for GA; SGA Small for GA.

It is unclear how or why exogenous glucagon could potentially cause metabolic acidosis in these patients. Endogenous glucagon facilitates hepatic lipolysis and fatty acid oxidation (15,16), which can produce ketone bodies, so perhaps exogenous glucagon could cause ketosis independent of glucose level. Ketones could potentially explain metabolic acidosis, but no patients had detectable ketones. However, this was a small sample size, as only 18 patients with metabolic acidosis had ketones checked (some multiple times) while on glucagon. It has been suggested in prospective studies that hypoglycemic newborns do not make high levels of ketones (17). Our findings, consistent with Miralles et al., show that no hypoglycemic neonates treated with glucagon were known to be in ketosis (6). Other potential etiologies suggested from glucagon drug reference materials could be vomiting or diarrhea, but these were not noted. The glucagon formulation does contain small amounts of lactose and hydrochloric acidic to adjust the pH, but no drug reference or product monograph have linked these to toxicity or acidosis (18). Finally, rat models suggest that glucagon may stimulate bicarbonate secretion in the distal tubule and collecting ducts, which then in theory could cause metabolic acidosis from bicarbonate losses; we are unaware of human studies (19). Only six subjects had a urine pH checked during the glucagon infusion, but none were alkalotic, ranging from 5.5 to 6.5 (20).

It is interesting that those with acidosis on glucagon were much lower birth weight and trended to have a lower birth weight percentile. SGA or growth restricted infants are a vulnerable population with reduced fat and glycogen stores, poor counter-regulation, and immature physiologic systems; up to 70% may have hypoglycemia, specifically hypofattyacidemic hypoketotic hyperinsulinemic hypoglycemia (21). One of the mechanisms by which glucagon elevates blood glucose is glycogenolysis (16,22). Growth restricted or smaller infants with reduced glucagon stores perhaps have less of a response to glucagon or are more vulnerable to potential metabolic side effects. We also found that non-IDM infants were more likely

to experience acidosis. IDM infants are the stereotypical HIH patients, but only made up about one quarter of our study cohort. These infants, who also tend to be larger term infants with normal glycogen stores, may respond better to glucagon with less detrimental side effects. Regardless of the mechanism, clinicians should be alerted to this potential association with metabolic acidosis when using glucagon infusions in neonates, especially in lower birthweight infants or the non-IDM population. Although we are not aware of direct harm of these episodes of compensated metabolic acidosis, there were indirect consequences in frequent workups for rare inborn errors of metabolism, adding to health care costs, blood draws with risk for anemia, and potential parental stress. If unexplained metabolic acidosis during glucagon therapy resolves with medication discontinuation, a workup is likely not indicated.

Like previous studies, we also showed a high frequency of thrombocytopenia in infants being treated with glucagon (6,7), although we acknowledge that thrombocytopenia is common in the NICU in general, especially in SGA babies (6), so this may not be causal; indeed over 10% of the total NICU admissions in our time frame captured thrombocytopenia as a diagnostic code, likely an underestimation as it relies on the provider listing the diagnosis. Based on our and previous data, it does appear that one should monitor platelet counts in infants on glucagon infusions. Hyponatremia, another common diagnosis in the NICU, which has been inconsistently reported in association with glucagon (7), was not frequent in our population, similar to Miralles (6).

Strengths of our study, considering the paucity of literature specific to glucagon use in hypoglycemic neonates, include a relatively large number of patients from the sole quaternary referral NICU in a sociodemographically diverse city. This series is the largest report of infants prescribed continuous glucagon infusions in the literature to our knowledge, as most others targeted specific groups like congenital hyperinsulinism, SGA, or premature infants with resistant hypoglycemia (3–6,8). The cohort spanned a short time frame with detailed glucagon dosing information and concomitant labs. Limitations include our single-centre retrospective study design without a control or non-exposed group, which does not allow for true association or causality, and limited information on true prevalence of metabolic acidosis in our NICU population (or really any NICU population) overall. Given the retrospective nature, not all infants had all desired labs available. Finally, 65% of the cohort was male. Although we did not find sex to be associated with any of our outcomes, and we would not have a biologic reason to believe that sex would affect response to glucagon, it is possible that this overrepresentation of male infants could have affected our results. Future studies could include a control group of hypoglycemic patients matched by diagnosis and other characteristics who were not prescribed glucagon, but study design, especially a prospective randomized controlled trial, is challenging as there are not copious alternative strategies for refractory hypoglycemia.

Overall, considering that the other limited therapies for refractory hypoglycemia have potential serious side effects, such as diazoxide's association with pulmonary edema and necrotizing enterocolitis (23), our study findings would not change our practice of utilizing glucagon infusion as an initial therapy. However, given the frequency of metabolic acidosis and thrombocytopenia in this retrospective cohort of hypoglycemic neonates prescribed glucagon infusions, monitoring of platelet counts, as well as consideration for delaying extensive metabolic workups for unexplained acidosis would be advised, especially in smaller infants and non-IDM subpopulations. More research is needed to elucidate potential mechanisms of glucagon therapy and metabolic acidosis in neonates.

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