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ARTICLE

The use of intramuscular glucagon to prevent IV glucose infusion in early neonatal hypoglycemia

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Abstract

Objective To investigate the success rate of intramuscular (IM) glucagon in preventing need for IV glucose and describe its glycemic effect.

Methods Retrospective study of 158 consecutive term neonates with feeding-resistant hypoglycemia treated with glucagon.

Results After glucagon, blood glucose (BG) increased in all but 1 infant by 25.9 ± 17.1, 42.1 ± 21.1, and 39.2 ± 28.3 mg/dL (1.4 ± 0.9, 2.3 ± 1.2, 2.2 ± 1.6 mmol/L) at 30, 60 and 120 mins respectively. In multivariable logistic regression, glucagon success was dependent upon gender (increased male risk) ($P = 0.021$), meeting American Academy of Pediatrics (AAP) criteria for immediate IV glucose ($P = 0.004$), birth weight, ($P = 0.018$) and delta glucose concentration at 60 min ($P = 0.013$). After IM glucagon, 24 out of 49 infants that met AAP criteria for immediate IV glucose (49%) ended up not requiring any additional intervention.

Conclusions Glucagon increases BG nearly universally in hypoglycemic infants and allowed reducing the number of infants that needed immediate IV glucose infusion therapy by ≈half.

Introduction

Neonatal hypoglycemia (NH) is a common condition affecting 5–15% of term infants [1–3]. Although prolonged or recurrent hypoglycemia may be associated with neurodevelopmental impairment, the evidence remains unclear as to whether or not asymptomatic, transient NH carries the same risks [4–7]. The American Academy of Pediatrics (AAP) recommends blood glucose (BG) screening only in infants with risk factors for NH [8]. We and others have, however, described significant rates of NH in both at-risk and risk-free infants [9, 10]. Using universal screening we found that 3.4% of normal neonates had BG levels below 40 mg/dL. While in the past, it was believed that the mechanism of transitional NH might be related to developmental delays in hepatic gluconeogenesis [11], the role of a low glucose threshold in neonates for insulin release has appeared to be at least equally important [12, 13].

Both definition of NH and clinical threshold for treatment are controversial [2, 8, 14]. In recent years, a BG concentration <47 mg/ dL (2.6 mmol/L) has been increasingly used to define NH, as lower concentrations have been associated with altered brain function and delayed neurodevelopment [15–17].

Treatment options for NH have included early and frequent feeding of breast milk or formula [18, 19] and feeding with added sugar [20]. However, oral intake during the first hrs of life is often low [21] and often does not always suffice to prevent or correct NH. Recently, intra-buccal dextrose gel has emerged as an effective and safe therapy for NH [22–24]. However, the absence of a newborn-specific product, and the use of over-the-counter diabetes-care products with poorly documented composition pose technical problems as they are not specifically intended for

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neonates [25]. When the enteral approach fails, IV dextrose is the next logical step, mandating admission to the NICU in most institutions [8].

Glucagon, a 29-amino-acid counter-regulatory hormone, can be a potent therapeutic alternative. A single dose of glucagon has been shown to enhance glycogenolysis, gluconeogenesis, and ketone formation [26, 27] and to have a marked glycemic effect when administered either intravenously or intramuscularly [27, 28]. Continuous intravenous glucagon infusion also has been recommended for the treatment of persistent NH [29]. Interestingly, publications on the use of single dose glucagon for NH are relatively scant. Most recent AAP guidelines on NH management fail to even mention glucagon as a therapeutic alternative [8]. Canadian guidelines recommend using continuous IV glucagon, but mention its use only in the management of severe or persistent NH mostly related to hyperinsulinism [30]. However, Neofax® mentions the use of Glucagon in neonates for the treatment of "hypoglycemia refractory to intravenous dextrose infusions" or "when dextrose infusion is unavailable" or in cases of "documented glucagon deficiency" [31]. Neofax states that glucagon may be administered subcutaneously, IM, ot IV push, at a dose to 200 mcg/kg/dose, with a maximum dose of 1 mg [31]. It also mentions that during continuous infusion, the rise in BG should occur within 1 h of starting infusion. A recent article in this Journal by Godin et al. [32] used doses that varied between 20 and 200 mg/kg and did not find significant differences in glycemic responses of infants who received more than 200 mg/kg and those who received <200 mg/kg.

In our own institution, a single dose IM glucagon has played a central role in the well-baby nursery management of neonates with NH for several years. It is used mainly in an attempt to prevent NICU admissions for IV glucose infusion.

We therefore conducted a retrospective study of glucagon use in our institution. We intended to describe the magnitude of the increase in BG concentration after glucagon administration, and to document whether this increase, if detected, is long-lasting. We aimed to investigate the success rate of intramuscular (IM) glucagon in preventing the need for IV glucose and subsequent NICU admissions, as well as to identify risk factors for failure. We hypothesized that the use of IM glucagon prevents NICU admission for IV glucose infusion in a substantial number of patients who met the AAP criteria for IV glucose.

Methods

This was an observational, retrospective study. It was approved by Shaare Zedek Institutional Review Board (SZMC-19-0093). Because of its retrospective aspect, the requirement for written informed consent was waived. The research data were collected from the electronic database of SZMC medical records.

NH screening protocol

Because in our institution the rates of NH a are nearly identical in infants traditionally considered to be at risk and among infants in neonates that were not thought to be at risk for NH [9], we practice universal screening for NH in all infants admitted to well-baby nurseries (WBN). Screening is performed within the first 2 h of life (most often within the first hour). This screening is performed using a drop of blood obtained from heel stick, deposited on a strip (Accu-check Inform II, Roche Diagnostics, GmbH, Mannheim, Germany) and read in an electronic reader of the same company. This particular point-of-care technology allows for fast (5 s) measurement of BG in a small sample volume (0.6 µL) and is largely unaffected by hematocrit [33]. Nearly 99% of values obtained with this instrument are within 12.5% of the mean hexokinase laboratory value [34]. Infants at low risk for NH and with an initial whole BG ≥ 50 mg/dL (2.8 mmol/L) are not monitored any further. In all infants with an initial screening BG < 50 mg/dL (2.8 mmol/L) and in those with risk factors for early NH, BG monitoring is continued for at least until 12 h of age, initially every 30 mins and gradually at longer intervals until at least two consecutive samples show concentrations above 50 mg/dL (2.8 mmol/L). The risk factors used for this selection are the ones adopted by the AAP [8] and include: infants who are either small for gestational age (SGA) or large for gestational age (LGA), infants born to mothers who have diabetes (IDMs), and late-preterm infants (born at a gestational age of 35–37 weeks).

Feeding protocol

Early feeding is offered to all infants. In order to promote breast feeding and to minimize early NH, infants are put to breast in the delivery room whenever possible. Upon admission to the WBN, infants found to have NH on initial screening are offered formula immediately, ad libitum, under strict BG monitoring as described above. Figure 1 summarizes our protocol for the screening and management of NH in the immediate post-partum period. In addition, infants with NH are fed and warmed in an incubator if found to be hypothermic (axillary temperature < 36.5 °C).

Management of NH

After infants with BG < 50 mg/dL (<2.8 mmol/L) are fed and warmed, additional therapies are offered based on repeated BG monitoring. If the initial BG is <30 mg/ dL

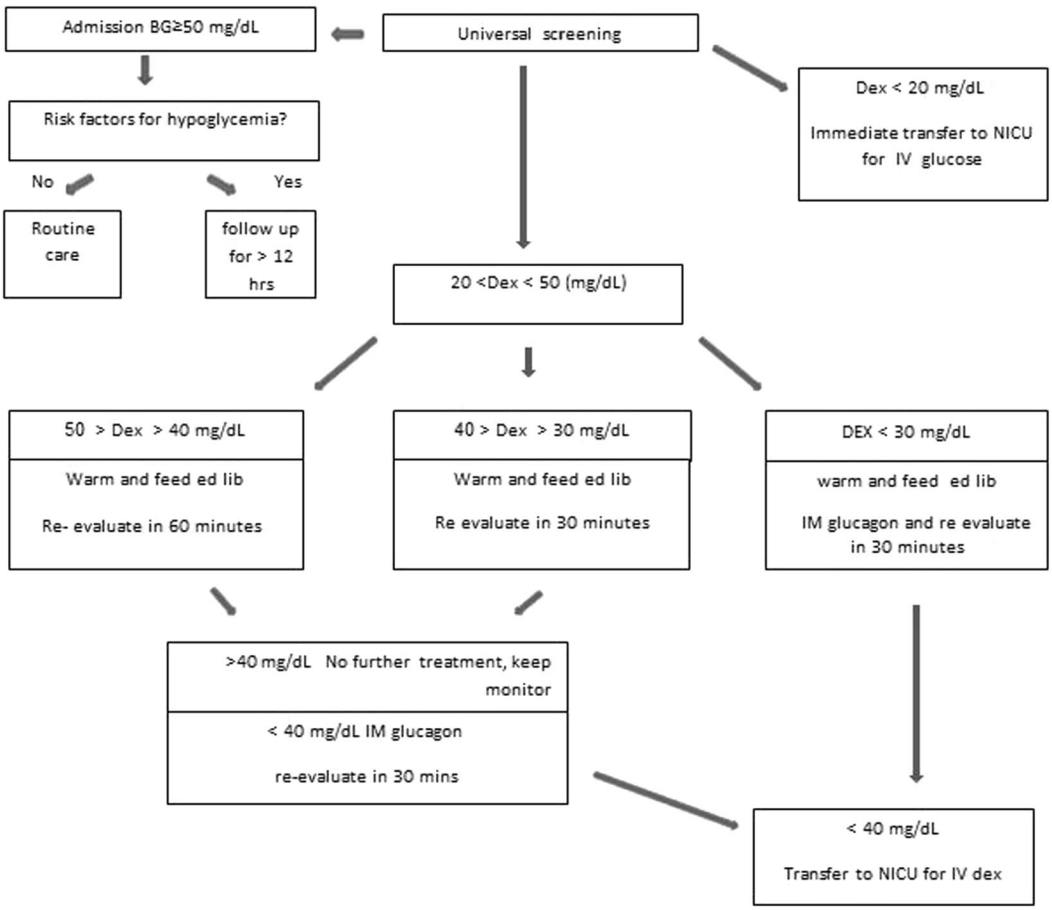

Fig. 1 Study clinical protocol. Immediate post-partum screening and management of hypoglycemia.

(1.7 mmol/L) or if during follow up despite feeding, the BG is <40 mg/dL Dl (2.2 mmol/L), IM glucagon is administered, and infants are left in the WBN for further monitoring. For convenience and in order to prevent errors in dosage during hypoglycemia, a single universal dose of 1 mg is administered. This therapy is not offered to infants born at a BW of <3.0 kg or to SGA infants, because we do not want to rely in such infants on their glycogen stores. Symptomatic infants, as defined by the AAP statement [8], (irritability, tremors, jitteriness, exaggerated Moro reflex, high pitched cry, lethargy, floppiness, cyanosis seizures, apnea, poor feeding), and infants that develop severe hypoglycemia (<20 mg/dL, 1.1 mmol/L) despite feedings are transferred to the NICU for immediate IV dextrose. Such infants may receive a single dose of IM glucagon pending the insertion of an IV line for glucose administration.

Data collection

We recorded the clinical course of all infants with NH, as well as demographic variables such as gestational age, infant gender, birth weight, date and hour of delivery, mode of delivery, singleton or multiple deliveries. We also recorded maternal morbidities such as diabetes mellitus, pregnancy associated hypertension, and maternal medications during pregnancy. For the purpose of analyses, NH was defined as a whole BG < 47 mg/ dL (2.6 mmol/L); we recorded all BG values obtained in all infants and the time at which they were obtained. In our analyses, we paid particular attention to the BG prior and closest to glucagon administration, and the BG values closest to 30 min, 60 min, 90 min and 120 min (according to written protocol) following glucagon administration. We also recorded the presence or absence of clinical symptoms, and any therapeutic support offered, such as feeding (type, amount, frequency), IV glucose, NICU admission or not.

Subjects

The study population consisted of a convenience sample of all consecutive infants treated with glucagon at SZMC during a period of 6 years from January 2013 to December 2018. We excluded infants with major congenital anomalies

(e.g., Down syndrome) and/or congenital infections (e.g., proven CMV infections, sepsis). We also excluded infants born at less than 36 completed weeks (these infants are routinely admitted to the NICU or intermediate unit). We categorized all infants by weight for gestational age as appropriate (AGA, 10–90th percentile for age), LGA (LGA, > 90th percentile for age) or SGA (SGA, < 10th percentile for age) using the national Israeli intrauterine growth curves [35]. We defined infants "theoretically" eligible for IV glucose according to AAP criteria as those who were symptomatic or hypoglycemic with a BG of <25 mg/dL (1.4 mmol/L) after two attempts of feeding during the first 4 h of life or <35 mg/dL (1.9 mmol/L) thereafter [8].

Outcomes

1. The magnitude of the increase in BG concentration after glucagon administration at different time intervals (30/60/120 mins after IM glucagon) detected, is long-lasting.
2. The success rate of IM glucagon in preventing the need for IV glucose and subsequent NICU admissions.

Statistical methods

The Minitab Statistical Package, version 16 (Minitab, State College, PA) was used for analyses. Data were tested for normality and continuous variables were expressed as mean ± 1 standard deviation (SD), or median and range as indicated by normality. Categorical variables were expressed as frequencies and percents. Association between two categorical variables was tested using Chi-square test or Fisher's exact test, while the comparison of continuous variables between groups was performed using either student *t* test or non-parametric Kruskal–Wallis test. All tests were two-tailed. Variables that were found to be possibly associated with the main outcome variable (need or not to administer IV glucose and NICU admission) at a P- *P* value ≤ 0.1 were entered into a multivariate model of logistic regression. Since all infants received the same 1 mg dose of glucagon regardless of their weight, we calculated a "glucagon dose" (1 mg/BW (kg)) for each patient. A *P* value of <0.05 was considered statistically significant.

Results

The study population analyzed included 158 consecutive infants all of whom reached the above mentioned criteria for IM glucagon administration during the study period. One hundred and six infants out of 158 (67%) had risk factors for hypoglycemia and would have been screen as per AAP guidelines [8].

Table 1 depicts selected demographic and clinical data of these infants and their mothers according their clinical response to IM glucagon and subsequent need for IV glucose. Briefly, non-responders were similar to responders in terms of gestational age, maternal diabetes or preeclampsia rates, non-reassuring fetal tracing, Apgar scores, breastfeeding rates, hypothermia, or enteral intake at the time NH was noted. They were however heavier on average, with a borderline higher rate of LGA infants. As per protocol, 100% of non-responders were admitted to NICU for IV glucose vs. 14% of the responders (mostly for observation, while they did not require IV glucose by definition) ($P < 0.0001$). There was a striking predominance of males in the overall population of infants, and males were more often non-responders to glucagon ($P = 0.022$). The vast majority of infants (153/158) in both groups were asymptomatic and no infant received emergency IV glucose because of symptomatic NH.

After IM glucagon administration, BG increased in all but one infant by a mean (SD) of 25.9 (17.1), 42.1 (21.1), and 39.2 (28.3) mg/dL [1.4 (0.9), 2.2 (1.6), 2.3 (1.2) mmol/L] at 30, 60 and 120 mins respectively. At 60 mins, the BG response to glucagon was correlated significantly with the glucagon dose (Fig. 2).

Table 2 depicts baseline and outcome metabolic data of these infants according to whether or not they "responded" to IM glucagon (i.e., ended up not getting IV glucose). Infants in both groups had similar age at first BG screening sample but mean BG at admission to WBN was slightly but significantly higher in responders. Initial BG just prior to glucagon IM, which was administered at an average age of about 4 h of life in both groups was also slightly but significantly higher in responders. Responders had significantly higher BG concentrations than non-responders at 30, 60 and 120 mins after glucagon IM. Although the difference (delta BG) between BG just prior to glucagon and BG after at 30 mins after glucagon was not significantly different between the two groups, it was much higher in the responders at 60 and 120 mins ($P < 0.0001$ and 0.023 respectively). Euglycemia ≥47 mg/dL (2.6 mmol/L) was achieved within 2 h of glucagon in 95.4% of responders vs. 85.4% of non-responders ($P = 0.047$). Length of stay (LOS) was much longer in non-responders (nearly twice as much, $P < 0.0001$). BG at discharge was higher in non-responders than in responders ($P = 0.002$). The increase in BG observed after glucagon was almost universal. In one single infant, BG decreased after glucagon IM by 16 mg/dL at 30 (1.6 mmol/L) mins, and was still 5 mg/dL (0.3 mmol/L) below the initial BG value at 60 min. This child was born by

Table 1 Selected demographic description of the patient population.

Variable	All patients $N = 158$	Responders $N = 109$	Non responders $N = 49$	p value
GA (SD)	38.7 (1.4)	38.6 (1.3)	38.8 (1.6)	0.45
Males (%)	102 (65)	64 (59)	38 (77)	0.022
Female (%)	56 (35)	45 (41)	11 (22)	
CS (%)	63 (40)	39 (36)	24 (49)	0.117
Birth weight (g)	3587 (510)	3341 (468)	3710 (558)	0.007
AGA (%)	109 (69)	73 (67)	36 (33)	0.056
LGA (%)	49 (31)	25 (51)	24 (49)	
Infant of diabetic mother (%)	58 (36)	40 (37)	18 (37)	0.996
Maternal preeclampsia (%)	2 (1.3)	1 (0.9)	1 (2.0)	0.316
Non-reassuring fetal tracing (%)	27 (17)	15 (13.8)	12 (24.5)	0.097
HTC capillary value > 75 (%)	6 (3.8)	5 (4.6)	1(2.0)	0.439
NICU admission	64 (41)	15 (14)	49 (100)	0.000
Apgar 1 min (median, range)	9 (4–9)	9 (4–9)	9 (6–9)	0.560
Apgar 5 min (median, range)	9 (8–9)	9 (8–9)	9 (8–9)	0.943
BG < 25 mg/dL	26 (16.4)	13 (11.9)	13 (26.5)	0.025
% breastfeeding at onset of feeding	133/139 (95.9)	93/97 (95.9)	40/42 (95.2)	0.865
Intake at hypoglycemic feeding (cc/feed)	22 (9.8)	22.9 (9.6)	20.4 (10.1)	0.273
Hypothermia (<36)	15 (9.4)	11 (10.2)	4 (8.3)	0.717

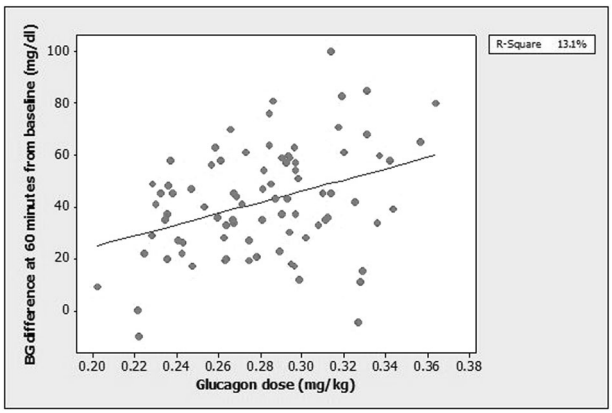

Fig. 2 Dose response to glucagon.

emergency cesarean because of suspected fetal distress at a gestational age of 39 weeks and a birth weight of 3.060 kg. He had an initial screening BG of 26 mg/dL (1.4 mmol/L) obtained at 0.37 h of life. He suffered from moderate meconium aspiration syndrome and was transferred immediately after birth to the NICU because of respiratory distress to the NICU, and not because of BG values. His BG was corrected only after an IV bolus of glucose, followed by a continuous IV glucose infusion.

In multivariable logistic regression taking into account gender, birth weight, AAP criteria for IV glucose, fetal distress, initial glucose and delta glucose 60 min after glucagon, the responsiveness to glucagon (no need for IV glucose) was dependent only upon gender ($P = 0.021$), meeting AAP criteria for IV glucose ($P = 0.004$), BW ($P = 0.018$) and delta glucose concentration at 60 min post glucagon ($P = 0.013$). From this analysis, we selected three risk factors for non-responsiveness: male gender, meeting AAP criteria for immediate IV glucose, and delta BG at 60 min below the mean delta response of 47 mg/dL (2.6 mmol/L). The absence of any of these criteria predicted a 100% response rate to glucagon, while the presence of at least 1, 2 or 3 criteria decreased the response rate to 93.7%, 67.7%, and 33.3% respectively.

Forty nine infants met the AAP criteria for immediate administration of IV glucose. They all, by design, received IM glucagon, and 24 (49%) did not require IV glucose and NICU admission.

Discussion

In this study, we described the BG responses of 158 consecutive AGA or LGA infants who reached our internal protocol for IM glucagon administration, i.e., because of an initial screening BG of <30 mg/dL (1.7 mmol/L), or because of initial BG ≥ 30 mg/dL and <40 mg/dL (≥1.7 and <2.2 mmol/L) and still <40 mg/dL at follow up despite feeding. Following glucagon IM, BG increased in all but one infant, indicating that, at the very least, glucagon IM may be used temporarily as a rescue therapy in face of severe hypoglycemia and when IV access is difficult. Theoretically, since

Table 2 Glucose indices at onset of screening and after intervention.

Variable	Responders[a] $N = 109$	Non responders[a] $N = 49$	p value
BG at admission to WBU (< 2 h) mg/dL [mmol/L]	38.7, (15.2) [2.1, (0.8)]	31.7, (10.3) [1.8, (0.6)]	0.001
Age (h) at admission G	0.9 (0.5)	1.0 (0.6)	0.800
Admission BG ≤ 25 mg/dL (1.4 mmol/L) (%)	13 (11.9)	13 (26.5)	0.025
Admission BG among infants with hypoglycemia mg/dL (mmol/L)	33.5, (7.0) [1.9, (0.4)]	30.1, (8.4) [1.7, (0.5)]	0.023
AAP criteria for Iglucose (%)	24/108 (22.2)	25/48 (52.1)	0.000
BG before Glucagon IM mg/dL (mmol/L)	33.6 ± 5.9 (1.9 ± 0.3)	30.6 ± 7.2 (1.7 ± 0.4)	0.019
Age (h) at Glucagon IM	4.3 (5.4)	4.6 (5.7)	0.704
**BG 30 min post Glucagon IM	60.6 (19.5) [3.4, (1.1)]	52.6 (20.4) (2.9, (1.1))	0.036
[c]Delta G 30 min post Glucagon IM	26.8 (17.5) [1.5 (1.0)]	24.016.4) [1.3 (0.9)]	0.422
**BG 60 min post Glucagon IM	82.0 (21.4) [4.6 (1.2)]	56.4 (21.2) [3.1 (1.2)]	0.000
[c]Delta G 60 min post Glucagon IM	47.3 (19.4) [2.6 (1.1)]	24.1 (16.7) [1.3 (0.9)]	0.000
**BG 120 min post Glucagon IM	75.4 (29.0) (4.2 ± 1.6)	61.7 (22.1) (3.4 ± 1.2)	0.007
[c]Delta G 120 min post Glucagon IM	42.5 (29.6) (2.4 ± 1.6)	29.7 (22.3) (1.6 ± 1.2)	0.023
Euglycemia (≥47 mg/Dl: 2.6 mmol/L) achieved within 2 H of glucagon IM (%)	104/109 (95.4)	35/41 (85.4)	0.047
LOS (median, range, hrs)	82 (36–313)	141 (54–826)	0.000
**BG at discharge	68.5 (12.3) [3.8 (0.7)]	75.0 (10.8) [4.2(0.6)]	0.002

G Stick Glucose result (mg/dL), *WBN* well-baby nursery, *GIR* glucose intake rate, *NA* not applicable.

[a]Responders were defined as patients who did not need IV glucose.

**mg/dL (mmol/L).

[c]"Delta" refers to change in BG (mg/Dl) from baseline.

this study was not randomized and placebo controlled, one may argue that the BG "response" which we have described may be unrelated to glucagon, and may rather represent the natural history of early NH. The significant BG dose response to glucagon at 60 and 120 mins supports that the rise in BG following glucagon had indeed been related to glucagon. We must point out, however, that the doses used in this study were pharmacologic and probably led to blood concentrations of glucagon exceeding by far physiologic concentrations. We noted that the larger the infant, the poorer the response to glucagon. All infants were given a glucagon dose of 1 mg IM regardless of their weight. Thus, when calculated per kg, the dose was actually largest in the smallest infants and smallest in the largest ones. It is also possible that many of the largest infants were LGA and may have had some degree of hyperinsulinism, which in turn may have affected the response to glucagon, rather than the glucagon dose per se. On the other hand, we note that the vast majority of patients had an increase in BG from baseline of greater than 30 mg/dL, which is traditionally a response noted in patients with hypoglycemia due to hyperinsulinism. This observation fits the theory that at the time of hypoglycemia these infants may have had some degree of relative hyperinsulinism [12, 13].

In this study, infants who ended up receiving IV glucose, i.e., defined by us as non-responders, were similar to responders in terms of gestational age, maternal diabetes or preeclampsia rates, non-reassuring fetal tracing, Apgar scores, breastfeeding rates, hypothermia, or enteral intake at the time NH was noted, but were heavier in average, with a borderline higher rate of LGA infants. We speculate that both lower glucagon dose per kg body weight and higher insulin baseline production may have played a role in this "non-response".

There was a striking predominance of males both in the overall population and in the sub-population of non-responders to glucagon ($P = 0.022$). This study is not the first one to report higher susceptibility of males to develop NH. The reason for this gender difference is unclear. It has been suggested by Bracero [36] that elevated testosterone concentration may produce insulin resistance [37] and may result in hyperplasia of the pancreas β islet cells, which then release increased amounts of insulin.

The vast majority of infants were asymptomatic. No infant received emergency IV glucose because of symptomatic NH. The fact that we performed universal screening may have led us to test mostly asymptomatic patients. However, hypoglycemia symptoms are notoriously non-specific, or subjective and insidious [38] and thus may not have been rigorously reported as such.

In multivariable logistic regression, gender, AAP criteria for immediate IV glucose, BW and delta glucose concentration at 60 min post glucagon were all significantly predictors of the need or not to administer IV glucose (our main outcome variable). The use of three criteria (male gender, AAP criteria for IV glucose, and delta BG at 60 mins below the mean delta response of 47 mg/dL) allowed to determine that the absence of any of these

criteria predicted a 100% response rate to glucagon; the presence of at least 1, 2 or 3 criteria decreased the response rate to 93.7%, 67.7%, and 33.3% respectively. Thus we suggest that, if glucagon is to be used in the management of NH, these risk factors could be used to better define the population that is the most likely to fail, and that may require more intensive monitoring.

An important finding of this report is that 49 infants met the AAP criteria for immediate administration of IV glucose. They all, by design, received IM glucagon, and 24 (49%) did not require the use of IV glucose and NICU admission. Thus, theoretically, glucagon use should prevent ~50% of IV glucose administration and subsequent NICU admission in these infants. The number needed to treat appears to be reasonable, as glucagon should be given to ~2 of these infants in order to avoid 1 NICU admission and IV therapy. This is not negligible, as separation from the mother predictably increases family anxiety and may have negative impact on breast feeding rates and duration, and may influence other long term outcomes as well [38]. Cost issues of an NICU admission are likely to also be important.

A limitation of our study is that its results are not applicable to infants born SGA since these infants were excluded from our glucagon protocol. We do not know if such infants, expected to have less hepatic glycogen storage would have an increase in BG following glucagon IM sufficient enough to justify this approach. Another limitation is that we used a point-of-care bedside measurement of BG rather than a hexokinase method using a laboratory-standard glucose measurement. However, as pointed out in the Methods section, the particular technology we used is very little influenced by hematocrit. Moreover, Harris et al. have recently shown that BG percentiles obtained by glucose oxidase based gas analyzers and those obtained by continuous interstitial glucose concentration measurements were in fact quite similar [39].

As expected, LOS was much longer in non-responders (nearly twice as much, $P < 0.0001$). The fact that BG at discharge was higher in non-responders than in responders is probably explained by differences in age at sampling time.

We conclude that BG increases nearly universally in infants following glucagon IM. The extent of this increase, meeting the AAP criteria for IV therapy, and male gender all are predictors of further need of IV glucose. The use of glucagon in our treatment algorithm enabled us to reduce by half the number of infants who would theoretically have needed immediate IV glucose infusion therapy. Future research should compare the efficacy and safety of IM glucagon vs. oral dextrose gel or vs. an additional dose of IM glucagon in the management of NH and their ability to prevent IV glucose administration and NICU admission. Although oral dextrose gel appears to be a promising minimally invasive method of preventing these events, it is not universally available. Commercial preparations of dextrose gel are tailored for adult diabetic patients and often contain additives less suitable or untested in neonates [25]. We suggest that at the very least, glucagon IM may be used temporarily as an efficient rescue therapy especially when hypoglycemia is severe and IV access difficult.

Author contributions Dr YK contributed to the concept and its realization, statistical analyses and writing of the paper. Ms OD contributed to the database collection and organization, and to the writing of the paper. Dr FBM contributed to the concept and its realization, statistical analyses and writing of the paper. Dr NW contributed to the concept and critical review of the paper. Drs CH contributed to statistical analyses and critical review of the paper. Drs ABN contributed to the realization of the project, troubleshooting of technical issues, and reviewed critically the paper. All authors reviewed the paper for important intellectual contents and approved the final version. All authors agree to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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