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Glargine co-administration with intravenous insulin in pediatric diabetic ketoacidosis is safe and facilitates transition to a subcutaneous regimen

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Abstract

Background—Diabetes ketoacidosis (DKA) is a common presentation and complication of type 1 diabetes (T1D). While intravenous insulin is typically used to treat acute metabolic abnormalities, the transition from intravenous to subcutaneous treatment can present a challenge. We hypothesize that co-administration of glargine, a subcutaneous long acting insulin analogue, during insulin infusion may facilitate a flexible and safe transition from intravenous to subcutaneous therapy.

Objective—To determine if the practice of administering subcutaneous glargine during intravenous insulin is associated with an increased risk of hypoglycemia, hypokalemia or other complications in children with DKA.

Methods—Retrospective chart review of patients aged 2-21 years, presenting to our center with DKA between April 2012 and June 2014. Patients were divided into two groups: those co-administered subcutaneous glargine with intravenous insulin for over 4 hours (G+); and patients with less than two hours of overlap (G−).

Results—We reviewed 149 DKA admissions (55 G+, 94 G−) from 129 unique patients. There was a similar incidence of hypoglycemia between groups (25% G+ vs. 20% G−, p=0.46). Hypokalemia (<3.5mmol/L) occurred more frequently in the G+ group (OR= 3.4, 95% CI 1.7-7.0, p=0.001). Cerebral edema occurred in 2/55 (3.6%) of the G− group and none of the G+ subjects.

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Conclusion—Co-administration of glargine early in the course of DKA treatment is well tolerated and convenient for discharge planning; however, this approach is associated with an increased risk of hypokalemia.

Keywords

diabetes; diabetic ketoacidosis; insulin; hypoglycemia; glargine

Introduction

Diabetic ketoacidosis (DKA) accounts for 65% of hospitalizations in pediatric patients with T1D and has a mortality rate between 0.15-0.31%,(1). One in four children with new-onset type-1 diabetes (T1D) present in DKA(2), and children with established T1D have an 8% annualized risk of developing this complication. This risk increases during adolescence(3). The management of DKA includes fluid resuscitation and intravenous insulin administration(4,5), followed by a transition to subcutaneous insulin. This transition is associated with an increased risk of hypoglycemia, rebound hyperglycemia, or other electrolyte abnormalities.

Commonly used intravenous insulin analogs have a half-life of less than 10 minutes(6). An appropriate overlap of subcutaneous insulin prior to discontinuing the insulin infusion is required to prevent rebound hyperglycemia and ketosis. Guidelines from the American Diabetes Association(7) and the International Society for Pediatric and Adolescent Diabetes(4) recommend subcutaneous insulin between 15 and 120 minutes prior to stopping the infusion. The recommended duration of co-administration depends on the pharmacokinetics of the particular insulin analogue used(4).

Multiple daily injection (MDI) regimens include once- or twice-daily administration of long-acting/basal insulin (e.g. detemir, glargine) in addition to mealtime administration of fast-acting insulin. The majority of patients treated for DKA receive subcutaneous long-acting basal insulin during the transition from intravenous insulin to a home regimen. Glargine and detemir provide a reasonably constant basal insulin action over 24 hours, and are generally dosed once a day(8-10), but the long duration of action of these basal analogs can present a challenge when transition from intravenous insulin happens outside of the usual basal dosing schedule. An example of this is where DKA resolves at 5 am, but family plans to give Lantus each night at 8 pm following discharge. Common approaches used to adjusting the timing of long acting insulin in the days following transition include: shifting the dose 2-4 hours per day to prevent significant insulin “stacking” and risk of hypoglycemia, or giving half of the basal insulin at the time of DKA resolution, followed by the full dose at the next appropriate routine dosing time.

Administering subcutaneous basal insulin at a predetermined time, in addition to receiving intravenous insulin, would facilitate a smooth and flexible transition to a home subcutaneous insulin regimen once DKA had resolved. This would allow all subsequent basal insulin injections to occur on schedule. For these reasons, a protocol that includes early administration of glargine with intravenous insulin has been established at our institution. The aim of this study was to determine if this practice of administering subcutaneous

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glargine during insulin infusion is associated with an increased risk of hypoglycemia, hypokalemia or other complications in children with DKA.

Methods

Children aged 2-21 years with pre-existing or new-onset T1D presenting to The Children's Hospital of Philadelphia (CHOP) emergency department in DKA between April 2012 and June 2014 were eligible for inclusion in this retrospective chart review. This study was approved by the Institutional Review Board at CHOP.

Patients were divided into distinct groups: those with pre-existing T1D, and those with new-onset T1D. In each group, children who received glargine ≥ 4 hours before discontinuation of intravenous insulin infusion (G+ group) were compared with those who received glargine ≤ 2 hours, or no subcutaneous insulin, before cessation of infusion (G− group). These time thresholds were chosen to ensure a detectable overlap in the insulin action of glargine with the insulin infusion in the G+ group, based on glargine pharmacokinetics(11).

Inclusion criteria were: at least one positive diabetes autoantibody (anti-insulin, anti-GAD65 or anti-ICA512), presence of DKA (defined below) and treatment with an intravenous insulin infusion. Exclusion criteria were: initiation of intravenous insulin outside of CHOP, hyperosmolar non-ketotic hyperglycemia (HHNK); treatment with systemic steroids; or a concurrent medical condition predisposing to ketosis (ie: metabolic disorders, growth hormone deficiency, adrenal insufficiency, ketotic hypoglycemia, or organic acidemia, ketogenic diet). No patient in our study required vasopressors for hemodynamic support.

The following data were extracted from medical records: age; sex; admission and discharge times; medical history including height, weight, duration of T1D, home insulin regimen, comorbidities; biochemical measurements during admission (A1C, glucose, pH, bicarbonate, potassium, blood urea nitrogen (BUN), pCO2, creatinine); insulin infusion start and end times; glargine dose and administration time. Serial glucose, bicarbonate and potassium measurements were collected for up to 24 hours after insulin infusion discontinuation.

DKA Treatment Protocol

At CHOP, the standard management of DKA is consistent with international recommendations(4). This includes fluid resuscitation, and an insulin infusion starting at 0.1 u/kg/hr. Glucose is measured hourly and serum potassium is measured every two hours, with intravenous fluid (IVF) concentrations titrated based on these results. IVF dextrose concentrations are titrated as follows: glucose > 300 mg/dL, no dextrose; glucose 200-300 mg/dL, 5% dextrose; and glucose <200 mg/dL, 10% dextrose; 12.5% dextrose used based on clinical discretion. Similarly, IVF potassium chloride or phosphate is titrated as follows: serum potassium > 6 mmol/L, 0 mEq/L; serum potassium 5.5-6 mmol/L, 20 mEq/L; serum potassium 4-5.4 mmol/L, 40 mEq/L; and serum potassium < 4 mmol/L, 60 mEq/L. When available, a 1:1 potassium chloride (KCl) to potassium phosphate (KPhos) ratio is used. Intravenous insulin is discontinued when bicarbonate concentration is greater than or equal to 16 mmol/L. In addition to this protocol, patients may receive a subcutaneous glargine

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dose of 0.3 - 0.5 u/kg/day on the first night during insulin infusion or soon before discontinuation of the insulin infusion if it has not already been administered.

Definitions

DKA was defined as pH < 7.3 or bicarbonate < 15 mmol/L, glucose concentration > 200 mg/dL and detectable urinary or serum ketones. We defined the resolution of acidosis as the time when serum bicarbonate concentration reached 16 mmol/L or higher. Hypoglycemia was defined as a blood glucose concentration < 60 mg/dL, on laboratory or point of care testing and occurring between the start of insulin infusion until 2 hours after it was stopped. Hypokalemia was defined as serum potassium concentration < 3.5 mmol/L from start of insulin infusion until 24 hours post discontinuation.

Laboratory Measurement

Biochemical tests were performed in the clinical chemistry laboratory at CHOP. Whole blood point of care (POC) Glucose was performed with a Nova meter (Nova Biomedical, Waltham, MA), which uses a modified glucose oxidase based amperometric test system with hematocrit and interference correction. Basic Metabolic Panel analytes and HbA1c were performed with a VITROS 5600 Integrated System (Raritan, NJ). Glucose was measured by glucose-oxidase coupled, colorimetric assay. Sodium was measured by direct potentiometry using methyl monensin as a sodium ionophore. Potassium was measured by direct potentiometry using valinomycin as a potassium ionophore. Bicarbonate was measured by carboxylation reaction coupled with reflectance spectrophotometry. BUN (BUN) was measured by colorimetric urease reaction. Creatinine was measured by creatine amidinohydrolase oxidation reaction coupled with colorimetric two-point rate densiometry. HbA1c was measured using spectrophotometry of hemolyzed whole blood, complexed with hexapeptide-glycan immunoglobulin. Urine ketones were measured by bedside sodium nitroprusside colorimetric reaction. Blood gas analytes including pH and pCO2 were measured using the RAPIDLab 1265 system (Siemens, Erlangen Germany).

Statistics

Standard descriptive statistics were used to summarize demographics, initial biochemical measures, time measures, and to determine the proportion of adverse events. All data were described by mean (SD). Normally distributed data, as determined by Shapiro-Wilk test were compared using Student's t-test. Skewed data were compared using Mann Whitney U tests (aka rank-sum test). Pearson's Chi-squared analysis or Fishers exact test was used to compare proportions. Sub-analysis of hypokalemia within the G+ new-onset patients, and its association with initial potassium level and glargine co-administration time, was done using logistical regression analysis. Statistical significance was defined using a 2-sided p-value <0.05 for all analyses. Statistical analysis was performed using SPSS 22.0 (IBM, New York, USA), Stata 14.1 (StataCorp, L.P., College Station, TX) and figures were generated using SPSS 22.0, Prism 5.0 (GraphPad Software Inc., California, USA), Microsoft Excel 16.0 (Microsoft, Washington, USA) and Adobe Illustrator 16.0 (Adobe Systems Inc., California, USA).

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Results

During the study period, there were 191 presentations of children in DKA, and 149 of these met inclusion criteria. Of the 42 excluded, 19 were outside of the age criteria, 6 did not have one or more autoantibody, and 5 had started DKA management at another institution, 2 had received glucocorticoids, and 10 episodes of DKA were not included in analysis because glargine co-administration was between 2 and 4 hours. There were 129 unique patients included some of whom had more than one DKA admission. Of the 149 episodes of DKA analyzed, 50 (34%) had new-onset T1D (31 G+, 19 G−) and 99 (66%) had pre-existing T1D (24 G+, 75 G−). Anthropomorphic and demographic characteristics, as well as baseline pH and bicarbonate concentration were similar between children in G+ and G− groups, both with new-onset and pre-existing T1D. The home insulin regimens for those with pre-existing T1D were MDI (28% G−, 75% G+), NPH (55% G−, 8% G+) or continuous subcutaneous insulin infusion (CSII) therapy (17% G−, 17% G+). The home insulin regimen for those with pre-existing T1D in the G+ group consisted of 75% using MDI, 8% using 70/30 or NPH, and 17% using CSII (Table 1). The insulin infusion rate (u/kg/hour) and total glargine doses (u/kg) were similar between new-onset and pre-existing T1D subgroups (Table 2). The duration of DKA and insulin infusion were longer in the G+ group (p=0.002). Mean duration of hospitalization was unaffected in new-onset (G+: 3.1 days and G−: 3.1 days, p=0.76) and pre-existing (G+: 1.9 days and G−: 1.7 days, p=0.73) T1D. Trends in acidosis resolution and glucose concentrations were similar in G+ and G− groups both for children with new onset and pre-existing T1D (Figure 1).

Hypoglycemia

The mean (SD) minimum glucose concentration during insulin infusion was lower in the G+ than the G− groups, although this did not reach statistical significance (G+: 84 (30) mg/dL, G−: 93 (38) mg/dl, p=0.24). No patient in either group experienced a severe complication of hypoglycemia such as seizure or loss of consciousness. The incidence of hypoglycemia was similar regardless of glargine co-administration in pre-existing (G+ 29%, G− 20%, p=0.4) and new-onset (G+ 22%, G− 21%, p=0.9) T1D (Table 2, Figure 2). The 1- and 2-hour post insulin infusion blood glucose trends were similar between groups (Figure 1A & 1B).

Hypokalemia

The mean initial potassium was 5.5 (G+) vs. 5.5 mmol/L (G−) (p=0.43) in those with pre-existing T1D and 4.5 (G+) vs. 4.9 (G−) mmol/L (p=0.13) in those with new-onset T1D (Table 2). The mean minimum potassium was 3.7 (G+) vs. 3.9 mmol/L (G−) (p=0.12) in those with pre-existing T1D and 3.1 (G+) vs. 3.5 (G−) mmol/L (p=0.02) in those with new-onset T1D (Table 2, Figure 2). In all patients, co-administration of glargine increased the odds of hypokalemia (OR=3.4, 95% CI 1.7-7.0), although this was not significant when patients with new onset (OR=3.0, 95% CI 0.91-10.2) or pre-existing diabetes (OR= 1.5 (0.5-4.5)) were analyzed separately.

In all patients, initial mean (SD) potassium was lower in children who had subsequent hypokalemia (4.8 (0.8) mmol/L vs 5.4 (0.8) mmol/L, p <0.01). Using logistic regression to correct for initial potassium in all patients, the odds of hypokalemia remained increased in

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the G+ group (OR 1.4, 95% CI 1.07-1.7). Serious adverse consequences of hypokalemia, such as cardiac arrhythmia, were not reported in any patient in this study.

Other outcomes

The duration of DKA was 10.9 (G+) vs. 6.6 (G−) hours (p=0.002) in those with pre-existing and 8.1 (G+) vs. 5.9 (G−) hours (p=0.06) in those with new-onset T1D. The rate of DKA resolution was measured by serum bicarbonate, which increased similarly between groups (Figure 1C & 1D). Two children included in this study had altered mental status with subsequent CT brain confirmation of cerebral edema. Both of these patients had pre-existing T1D and were in the G− group.

Discussion

Early administration of glargine in children with DKA prepares the patient for a convenient and expeditious transition to post-discharge long acting subcutaneous insulin(12). Thus, the premise of this study was that this may be a preferred method of supporting transition to subcutaneous insulin for children with DKA, provided it is safe. We have shown that the early co-administration of glargine with an intravenous insulin infusion is not associated with an increased risk of hypoglycemia or cerebral edema but may confer an increased risk of hypokalemia. This may be more pronounced in children with lower initial potassium concentration at presentation.

Co-administration of subcutaneous glargine with intravenous insulin has only been reported in 4 previous studies; Houshyar et al (mean age: 29, 82% T1D), Doshi et al (mean age: 40, 40% T1D), Hsia et al (mean age: 43, 52% T1D), and Shankar et al (mean age: 13, 100% T1D)(13-16). Three studies showed shorter DKA and hospital duration times(13,14,16). One study showed an increase in hypoglycemia and hypokalemia(13), while no study suggested an increased risk of cerebral edema.

Additional studies have addressed the effect of insulin dose in DKA on hypoglycemia, hypokalemia, resolution of acidosis and incidence of cerebral edema. A study comparing 1 u/kg/hr with 0.1 u/kg/hr intravenous insulin in children with DKA revealed higher rates of hypokalemia (62% vs. 18%) and hypoglycemia with higher insulin doses(17). Another study comparing 0.1 u/kg/hr with 0.05 u/kg/hr also reported an increased risk of hypokalemia with higher insulin doses (48% vs. 20%), but also showed an increased risk of hypoglycemia (20% vs. 4%). Higher insulin doses did not result in a faster resolution of DKA, which is in agreement with our data(18).

Our study includes the largest number of pediatric patients to date with prolonged co-administration of subcutaneous glargine with intravenous insulin. We have confirmed that early glargine co-administration does not significantly increase the risk of hypoglycemia. A plausible explanation is that the careful monitoring and management of glucose concentrations in children during insulin infusion is likely to result in the prevention of hypoglycemia through the proactive increase in intravenous dextrose concentration. We did find an increased occurrence of hypokalemia in children with glargine co-administration; however, there were no clinical complications of hypokalemia noted in any included patient.

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The limitations of our study are related to its retrospective and non-randomized design. It is not possible to determine if additional clinical factors or severity of metabolic abnormalities may have influenced the supervising clinician's decision to withhold or administer glargine early in the course of DKA. While most parameters were generally comparable between G+ and G− patients, there were significant differences in the duration of acidosis, duration of intravenous insulin infusion, and baseline BUN concentration. Longer duration of acidosis was seen in the G+ group, which may reflect selection bias in children meeting the criteria for glargine co-administration ≥ 4 hours from the end of insulin infusion. This may account for the similar duration of hospitalization in the G+ and G− groups, making it difficult to determine if this approach shortened hospital admission for children with pre-existing T1D. All patients with new-onset T1D are routinely admitted for a minimum 3-day hospital stay and educational program, which may account for the similar duration of admission in these G+ and G− patients. While a randomized controlled trial would provide stronger evidence for the efficacy of this approach, we have not identified risks that would restrict glargine co-administration in clinical practice.

In conclusion, we have shown that the practice of co-administering long-acting subcutaneous insulin and intravenous insulin to increase the incidence of hypokalemia. Because there were no clinical complications in our population we believe this practice to be safe and we have found it to facilitate a smooth transition from inpatient to outpatient management. However, if this approach is used, we recommend that clinicians are aware of an associated increased risk of hypokalemia.

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Abbreviations

BUN	Blood Urea Nitrogen
CHOP	The Children's Hospital of Philadelphia
CSII	Continuous Subcutaneous Insulin Infusion
DKA	Diabetic Ketoacidosis
G+	Group receiving glargine ≥ 4 hours before discontinuation of intravenous insulin
G−	Group receiving glargine ≤ 2 hours before discontinuation of intravenous insulin
T1D	Type 1 Diabetes

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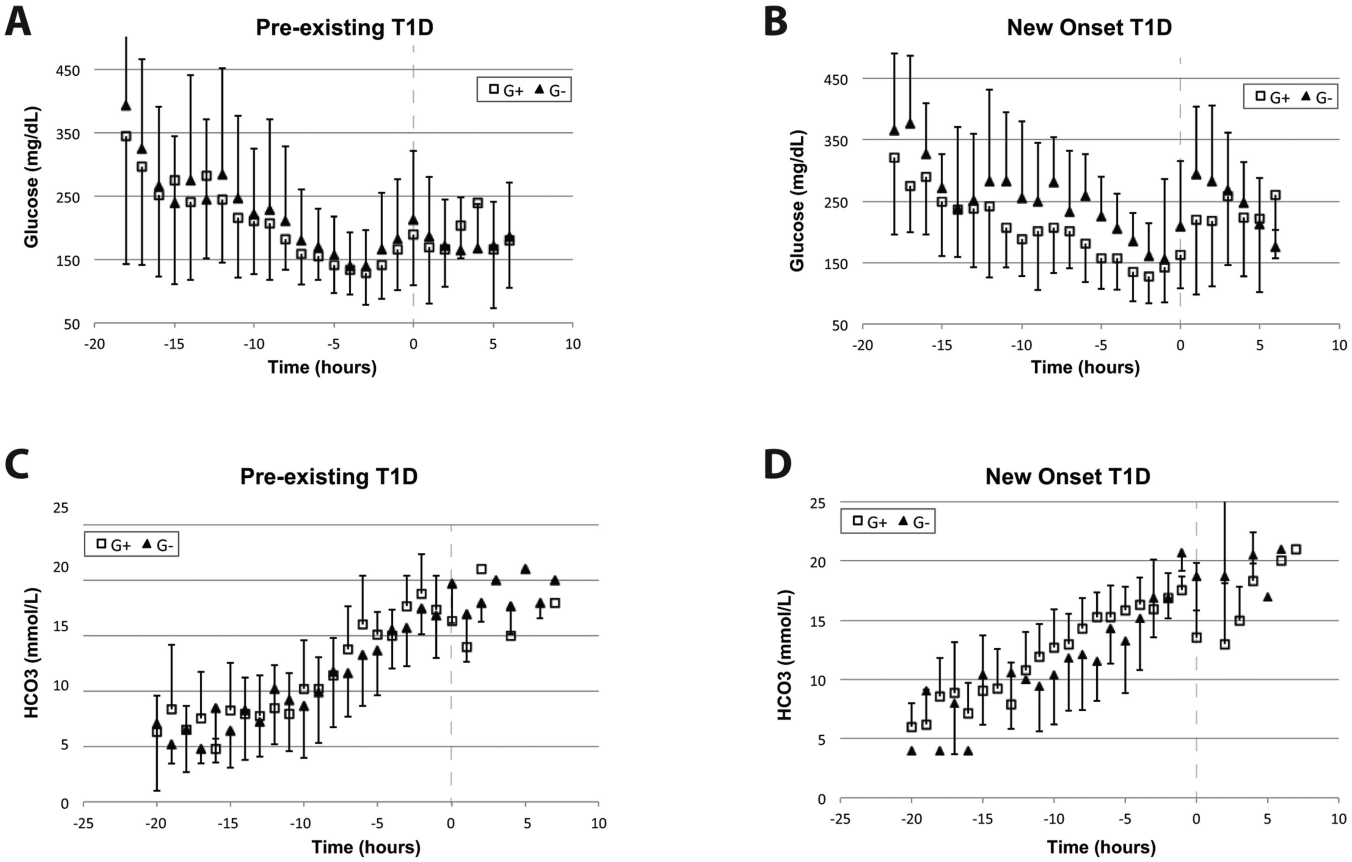

Figure 1.

Hourly trend of glucose (A & B) and serum bicarbonate (C & D) values for pre-existing or new-onset T1D. Error Bars represent standard deviation. Children who received glargine ≥ 4 hours (G+) or ≤ 2 (G−) hours before the end of the insulin infusion are represented by open squares or filled triangles respectively. The end of the insulin infusion is marked by 0 hours on the x-axis.

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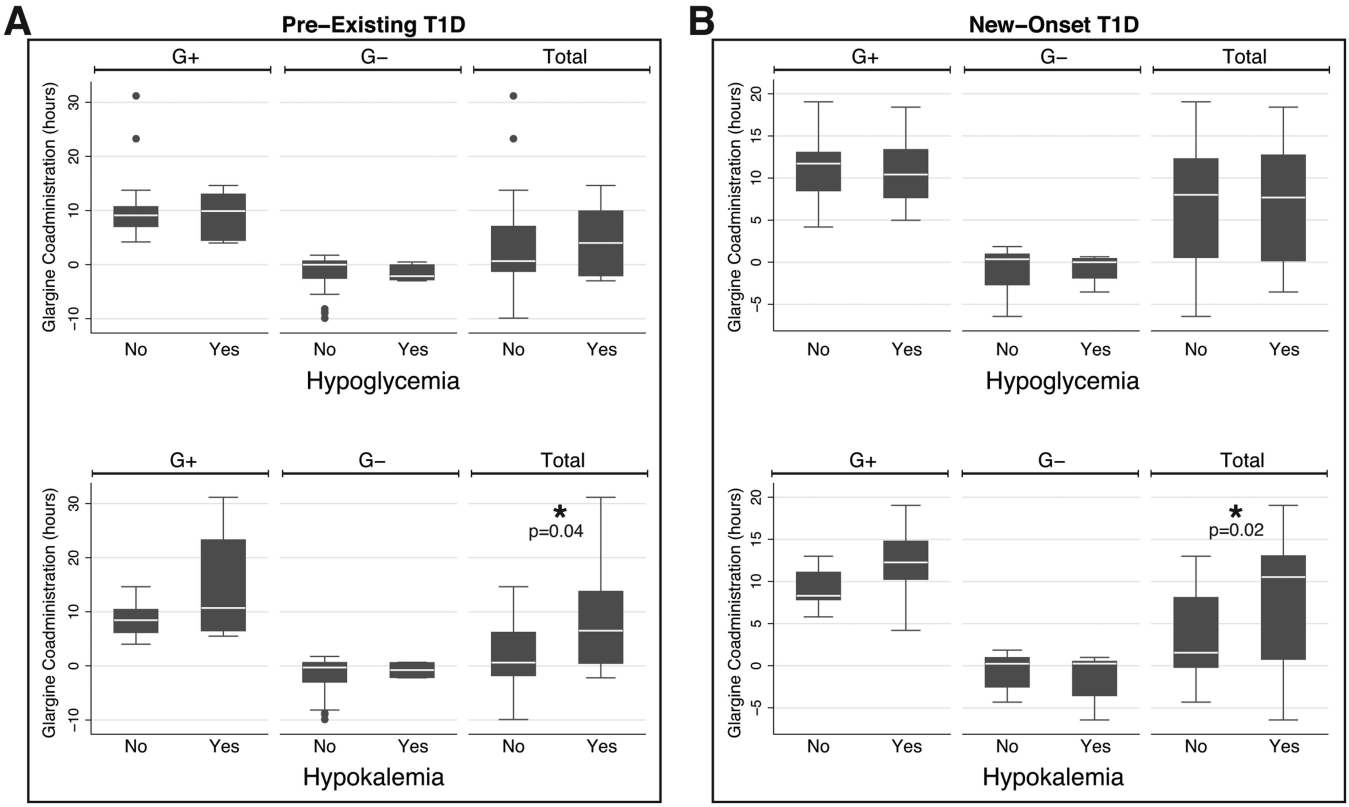

Figure 2.

Standard Boxplots with whiskers of hypoglycemia and hypokalemia incidence occurring as a function of glargine co-administration time in patients with pre-existing (A) and new-onset (B) TID. Hypoglycemia is defined as glucose <60 mg/dL. Hypokalemia is defined as potassium <3.5 mmol/L. Children who received glargine ≥ 4 (G+) or ≤ 2 (G−) hours before the end of the insulin infusion are subdivided into columns.

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Table 1

Demographics, Anthropomorphic Data and Baseline laboratory measurements in children with new-onset and pre-existing type 1 diabetes, separated according to the timing of glargine administration relative to stopping insulin infusion.

	Pre-existing T1D (n=99)			**New-Onset T1D (n=50)**		
	G+ Glargine ≥ 4 hours	**G− Glargine ≤ 2 hours**	**p-value**	**G+ Glargine ≥ 4 hours**	**G− Glargine ≤ 2 hours**	**p-value**
Number (n)	24	75		31	19	
Male (%)	33%	47%	0.25	39%	53%	0.34
Age (years)	15.0 (2.6)	14.3 (3.4)	0.42	9.7 (2.5)	10.2 (4.1)	0.36
Height (cm)	157.4 (25.4)	152.7 (21.1)	0.08	140.1 (14.3)	139.8 (23.6)	0.91
Weight (kg)	59.5 (15.0)	50.7 (14.7)	**0.02**	33.4 (12.5)	34.1 (12.5)	0.82
BMI (kg/m^2)	22.2 (5.3)	21.2 (4.4)	0.63	16.8 (3.7)	16.8 (2.6)	0.41
Duration of Diabetes (years)	6.9 (3.8)	7.4 (3.5)	0.65	n/a	n/a	n/a
Basal Bolus Home Regimen (n,%)	18, 75%	21, 28%	<0.01 $^{\phi}$	n/a	n/a	n/a
pH	7.11 (0.10)	7.15 (0.12)	0.11	7.17 (0.09)	7.19 (0.07)	0.27
HCO3 (mmol/L)	5.0 (2.7)	6.7 (4.0)	0.09	6.3 (3.2)	7.7 (2.8)	0.09
pCO2 (mmHg)	24.0 (5.4)	27.2 (8.0)	0.14	21.7 (6.1)	26.0 (6.6)	**0.04**
Corrected Na (mmol/L) $^{\Psi}$	146.7 (4.3)	147.4 (6.4)	0.64	145.2 (5.1)	145.9 (6.1)	0.50
BUN (mg/dL)	17.6 (9.3)	17.3 (4.6)	0.48	11.8 (5.0)	15.9 (6.2)	**0.004**
Creatinine (mg/dL)	0.87 (0.35)	0.82 (0.28)	0.40	0.55 (0.20)	0.64 (0.27)	0.27
HbA1c (%)	11.4 (2.0)	11.2 (2.0)	0.70	12.2 (1.8)	11.3 (2.3)	0.26
HbA1c (mmol/mol)	101 (22)	99 (22)		110 (20)	101 (25)	

Median (SD) presented. P-values obtained using mann-whitney u-test.

$^{\phi}$calculated using Pearson chi-square.

$^{\Psi}$[Corrected Sodium = Measured sodium + 0.024 × (Serum glucose - 100)] as defined by Hillier Method(19).

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Table 2

Treatment and Complications in children with new-onset and pre-existing T1D, separated according to the timing of glargine administration relative to stopping insulin infusion.

	Pre-existing T1D (n=99)			New-Onset T1D (n=50)		
	G+ Glargine ≥ 4 hours	**G− Glargine ≤ 2 hours**	**p-value**	**G+ Glargine ≥ 4 hours**	**G− Glargine ≤ 2 hours**	**p-value**
Number (n)	24	75		31	19	
Duration of Acidosis (hours)	10.9 (7.4)	6.6 (4.0)	**0.002**	8.1 (4.2)	5.9 (3.6)	0.06
Duration of iv insulin (hours)	16.4 (8.3)	11.2 (6.2)	**0.002**	15.5 (5.6)	10.0 (5.5)	**0.002**
Duration of glargine co-administration (hours)	10.2 (6.1)	n/a	n/a	11.3 (3.7)	n/a	n/a
Insulin Infusion Rate (u/kg/hr)	0.0996 (0.002)	0.0987 (0.007)	1.0	0.096 (0.015)	0.099 (0.006)	0.83
Glargine dose (u/kg)	0.36 (0.16)	0.40 (0.14)	0.46	0.44 (0.10)	0.37 (0.13)	**0.03**
Initial Serum Glucose (mg/dL)	488 (164)	497 (193)	0.78	505 (123)	509 (121)	0.83
Minimum Glucose (mg/dL)	85 (36)	92 (38)	0.52	84 (26)	102 (38)	0.13
[#]Hypoglycemia (n)	29% (7)	20% (15)	0.35[ϕ]	22% (7)	21% (4)	0.90[ϕ]
Initial potassium (mmol/L)	5.5 (1.0)	5.5 (0.9)	0.43	4.5 (0.5)	4.9 (0.8)	0.13
Minimum potassium (mmol/L)	3.7 (0.7)	3.9 (0.6)	0.12[Ω]	3.1 (0.5)	3.5 (0.6)	**0.02** [Ω]
[##]Hypokalemia (n)	25% (6)	19% (14)	0.50 [ϕ]	71% (22)	47% (9)	0.10 [ϕ]
Cerebral Edema (n)	0	3% (2)	0.42 [ϕ]	0	0	n/a
Hospital Admission Duration (days)	1.9 (1.1)	1.7 (0.8)	0.73	3.1 (0.4)	3.1 (0.6)	0.76

Mean (Standard Deviation) presented unless otherwise stated.

P-values calculated using mann-whitney u-test unless otherwise specified.

[#]Hypoglycemia defined as glucose <60 mg/dL.

[##]Hypokalemia defined as potassium <3.5 mmol/L. Patients in the G+ group with hypokalemia prior to receiving glargine were not included in this analysis.

[Ω]Calculated using students t-test.

[ϕ]calculated using Pearson chi-square.