Insulin Dosing in Diabetic Ketoacidosis: Less May Be More

Source: *Nallasamy K, Jayashree M, Singhi S, et al. Low-dose vs standard-dose insulin in pediatric diabetic ketoacidosis: a randomized clinical trial. JAMA Pediatr. 2014;168(11):999-1005; doi:10.1001/jamapediatrics.2014.1211*

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Question: Among children ≤12 years old with diabetic ketoacidosis, does low dosing of regular insulin achieve equally effective outcomes compared to standard dosing?

Question type: Treatment

Study design: Randomized controlled trial

Investigators from the Postgraduate Institute of Medical Education and Research in India conducted a randomized controlled trial to determine if a dosing of regular insulin that is lower than the currently recommended dose could be safely and effectively used in children with diabetic ketoacidosis (DKA). Eligible participants were children ≤12 years of age who presented to the emergency department of a tertiary teaching hospital with DKA. DKA was defined as the presence of hyperglycemia (blood glucose [BG] ≥200 mg/dL), acidosis (a pH <7.3 or bicarbonate <15 mEq/L), and ketonuria (urine dipstick ≥2+). Children with severe symptoms such as anuria, shock, and mental status changes were excluded.

Study children were randomized to receive either regular insulin at the standard recommended dose (0.1 U/kg per hour) or at a low dose (0.05 U/kg per hour). All participants received fluid resuscitation and rehydration per hospital protocol, which included replacement of deficit fluids (routinely estimated at 65 ml/kg) over 36 hours and an additional 20 ml/kg bolus of isotonic saline in those with poor perfusion. Dextrose (5%) was added to IV solutions when the BG was <250 mg/dL and titrated to maintain a BG level of 180-220 mg/dL. Laboratory measurements included hourly BG and every-4-hour assessment of serum electrolytes, urea, creatinine, urine ketones, and venous blood gas. Demographic and clinical characteristics of participants were also collected.

The primary outcome was the rate of decrease in BG until the BG level reached ≤250 mg/dL. The low dose was considered noninferior to the standard dose if the difference in mean BG reduction between low and standard dose participants did not exceed 18 mg/dL per hour. Secondary outcomes included time to resolution of acidosis, episodes of treatment failures, and incidence of hypokalemia and hypoglycemia.

There were 50 participants enrolled, with 25 randomized to each insulin dose group. Demographic and clinical characteristics of participants in the 2 dosing groups were similar, including mean BG concentrations when therapy started (485 mg/DL for the low dose group vs 524 mg/dL for those in the standard dose group) as well as volume and sodium content of fluids administered.

There was no significant difference between the low and standard dose groups in the rate of decrease in BG (difference between means: 7.2 mg/dL per hour; 95% CI, -19 to 4.7). Similarly, there was no significant difference in time to resolution of acidosis. There was a nonsignificant trend toward fewer episodes of hypokalemia among those in the low dose group (20% vs 48%; $P = .07$), but no statistically significant difference in the rate of hypoglycemia (4% and 20% respectively; $P = .17$) between the 2 treatment groups. Only 1 child, in the standard dose group, developed cerebral edema. Treatment failures did not differ by treatment groups.

The investigators conclude that low dose insulin was not inferior to standard dosing in pediatric DKA.

Commentary by

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Dr Kirkland has disclosed no financial relationship relevant to this commentary. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

DKA is a common complication of type 1 diabetes mellitus (DM1). Approximately 25% of newly diagnosed diabetics present in DKA[1] and 1%-10% of those with established DM1 present with DKA each year.[2] Death is uncommon (0.15%) and primarily related to cerebral edema.[2] Treatment of DKA involves fluid resuscitation to reverse hypoperfusion and insulin therapy to normalize BG levels and suppress lipolysis and ketogenesis.[1] Consensus guidelines recommend an IV insulin infusion of 0.1 U/kg per hour until resolution of ketoacidosis.[1,2]

Investigators of the current study tested if a lower dose of insulin (0.05 U/kg per hour) is adequate to reverse DKA. Some authors have previously reported success with lower insulin doses,[3,4] with the hypothesis being that this dose still results in a high enough plasma insulin level to offset the hepatic resistance to insulin that occurs in DKA but causes a more gradual decrease in BG and less drastic electrolyte shifts (and, therefore, fewer adverse events). However, in another study, investigators compared children treated at 2 centers with different insulin doses (0.1 vs 0.025 U/kg per hour).[5] Those treated with the lower dose had a longer duration of acidosis and delayed normalization of BG.

The current study provides compelling evidence that the rate of BG decrease is not significantly different between low and standard insulin dosing. The study, however, was not adequately powered to detect differences in secondary outcomes, and lack of blinding of providers and participants to the treatment group could have introduced treatment bias. While a practice change is not yet indicated, further trials with larger sample sizes seem like a reasonable next step.

References

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Key words: diabetic ketoacidosis, cerebral edema, insulin therapy

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ISSN Numbers
Print: 1099-6605
Online: 1556-362X

Customer Service and Renewals: (866) 843-2271.
Email Address: grandrounds@aap.org
Subscription Rates: AAP member $102/year; non-member $127/year (12 issues), including up to 18 *AMA PRA Category 1 credit(s)*™.

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