Low-Dose vs Standard-Dose Insulin in Pediatric Diabetic Ketoacidosis
A Randomized Clinical Trial

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IMPORTANCE The standard recommended dose (0.1 U/kg per hour) of insulin in diabetic ketoacidosis (DKA) guidelines is not backed by strong clinical evidence. Physiologic dose-effect studies have found that even lower doses could adequately normalize ketonemia and acidosis. Lowering the insulin dose may be advantageous in the initial hours of therapy when a gradual decrease in glucose, electrolytes, and resultant osmolality is desired.

OBJECTIVE To compare the efficacy and safety of low-dose insulin against the standard dose in children with DKA.

DESIGN, SETTING, AND PARTICIPANTS This was a prospective, open-label randomized clinical trial conducted in the pediatric emergency department and intensive care unit of a tertiary care teaching hospital in northern India from November 1, 2011, through December 31, 2012. A total of 50 consecutive children 12 years or younger with a diagnosis of DKA were randomized to low-dose (n = 25) and standard-dose (n = 25) groups.

INTERVENTIONS Low-dose (0.05 U/kg per hour) vs standard-dose (0.1 U/kg per hour) insulin infusion.

MAIN OUTCOMES AND MEASURES The primary outcome was the rate of decrease in blood glucose until a level of 250 mg/dL or less is reached (to convert to millimoles per liter, multiply by 0.0555). The secondary outcomes included time to resolution of acidosis, episodes of treatment failures, and incidences of hypokalemia and hypoglycemia.

RESULTS The mean (SD) rate of blood glucose decrease until a level of 250 mg/dL or less is reached (45.1 [17.6] vs 52.2 [23.4] mg/dL/h) and the mean (SD) time taken to achieve this target (6.0 [3.3] vs 6.2 [2.2] hours) were similar in the low- and standard-dose groups, respectively. Mean (SD) length of time to achieve resolution of acidosis (low vs standard dose: 16.5 [7.2] vs 17.2 [7.7] hours; \( P = .73 \)) and rate of resolution of acidosis were also similar in the groups. Hypokalemia was seen in 12 children (48%) receiving the standard dose vs 5 (20%) of those receiving the low dose (\( P = .07 \)); the tendency was more pronounced in malnourished children (7 [88%] vs 2 [28%]). Five children (20%) and 1 child (4%) receiving standard- and low-dose infusion (\( P = .17 \)), respectively, developed hypoglycemia. Treatment failure was rare and comparable. One child in the standard-dose group developed cerebral edema, and no deaths occurred during the study period.

CONCLUSIONS AND RELEVANCE Low dose is noninferior to standard dose with respect to rate of blood glucose decrease and resolution of acidosis. We advocate a superiority trial with a larger sample size before 0.05 U/kg per hour replaces 0.1 U/kg per hour in the practice recommendations.

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Diabetic ketoacidosis (DKA) accounts for 8% to 29% of all primary diabetic admissions to a hospital, thus contributing to high costs of care for children with type 1 diabetes mellitus. Fluid correction and insulin therapy are the cornerstones of DKA management. Although rehydration alone can cause partial correction of hyperglycemia, insulin is required to normalize hyperglycemia and suppress lipolysis and ketogenesis. Insulin therapy has evolved during 4 decades in an attempt to identify a perfect dose that will not only correct ketoacidosis but also do so without complications. The earlier high-dose (1 U/kg per hour) and bolus insulin therapies went out of vogue after studies indicated that a similar therapeutic response, albeit with minimal adverse effects, could be achieved with a dose of 0.1 U/kg per hour. Thereafter, continuous insulin infusion at 0.1 U/kg per hour became standard of care in the management of DKA despite not having strong clinical evidence of its superiority over lower doses. A few articles have highlighted the utility of insulin doses lower than the standard recommended one. Noyes et al observed that insulin doses of 0.03 and 0.05 U/kg per hour could adequately normalize ketosis in DKA. Puttha et al and Al Hanshi and Shann, in their respective pediatric studies, have reported that a dose of 0.05 U/kg per hour was as effective as the standard dose in correcting acidosis.

It is a well-established fact that resolution of acidosis and not blood glucose (BG) reduction determines the end point of DKA therapy. However, much of the discussion in DKA management throughout the years has centered around the initial hours of therapy, with a focus on sodium, water, BG decrease, and their effect on rapid osmolar shifts. Although rapid BG decrease by itself has not been conclusively proven to be a risk factor for cerebral edema, some authors have reported a rapid decrease in BG with the use of doses greater than 0.05 U/kg per hour. In addition, some have found a more gradual reduction in plasma osmolality due to slower decrease in BG in children treated with 0.05 U/kg per hour compared with 0.1 U/kg per hour of insulin. The insulin-induced intracellular shift of glucose results in a non-equimolar increase in serum sodium; the sodium level increases less than the BG level decreases. Rapid BG decreases can cause an attenuated increase in serum sodium, producing a greater than expected decrease in osmolality.

Therefore, some authors believe that lowering or delaying the insulin dose may cause a gradual decrease in BG and a gentle electrolyte shift. Moreover, in developing economies, children with DKA may also benefit from a lower insulin dose because associated comorbidities, such as malnutrition, carry a high risk of therapy-related hypokalemia and hypoglycemia. Given this background and the lack of prospective studies testing lower insulin dose, we planned this trial to compare low-dose with standard-dose insulin with respect to rate of BG decrease, time to resolution of acidosis, episodes of treatment failure, and incidence of hypokalemia and hypoglycemia in children with DKA.

Methods

Study Design and Participants
The study was approved by the Institute Ethics Committee of the Postgraduate Institute of Medical Education and Research. Written informed consent was obtained from the parents. This was a prospective, open-label randomized clinical trial conducted in the pediatric emergency department and intensive care unit of a tertiary care teaching hospital from November 1, 2011, through December 31, 2012. All consecutive children 12 years or younger who presented with DKA defined as hyperglycemia (BG >200 mg/dL [to convert to millimoles per liter, multiply by 0.0555]), acidosis (pH <7.3 or bicarbonate <15 mEq/L [to convert to millimoles per liter, multiply by 1]), and ketonuria (urine dipstick test result ≥2+) were enrolled. Children with symptomatic cerebral edema, septic shock at presentation, anuria for longer than 6 hours, and insulin treatment before admission were excluded.

Randomization
Eligible children were enrolled at 1 hour of admission after receiving the rehydrating fluid during the first hour. A web-generated random number sequence was used to randomize them into 2 groups. The allocation was concealed in opaque, brown, sealed envelopes, which were kept with a health care worker not involved in any other aspect of the study. The patient assignment was made by opening the numbered envelopes only after obtaining written informed consent. Each envelope contained a slip that listed I (for the low-dose protocol) or II (for standard-dose protocol). The participants and those administering the interventions were, however, not masked to group assignment.

Intervention
Insulin therapy was started as a continuous intravenous infusion using an infusion pump. The low-dose group received regular insulin at 0.05 U/kg per hour, whereas the standard-dose group received insulin at 0.1 U/kg per hour. Correction of acidosis (pH ≥7.3 and bicarbonate ≥15 mEq/L) was taken as the end point, and patients thereafter were shifted to subcutaneous regular insulin with an overlap of 30 minutes.

Procedures
Patients were managed as per the unit’s current protocol for DKA. Fluid volume was calculated as a sum of deficit (65 mL/kg) and maintenance for 36 hours. Children who presented with evidence of hypoperfusion or hypotensive shock received an additional 20 mL/kg of isotonic saline for 1 hour. Isotonic (0.9%) saline was used as rehydrating fluid for at least the initial 6 hours and changed to half normal (0.45%) saline based on serum sodium and corresponding effective osmolality. Dextrose (5%) was added to rehydrating fluid once the BG level decreased to 250 mg/dL or less and the concentration titrated to maintain a BG level between 180 and 220 mg/dL. Potassium chloride (40 mEq/L) was added to rehydrating fluid immediately after resuscitation to maintain a serum potassium level between 3.5 and 5.5 mEq/L (to convert to millimoles per liter, multiply by 1).

Monitoring
Capillary or venous BG was checked every hour or more frequently, depending on clinical need (Optium Xceed glucometer; Abbott Diabetes Care Inc). Readings above the gluco-
eter range were counterchecked by serum BG measurement using the hexokinase method. Serum electrolytes, urea, creatinine, urine ketones, and venous blood gas were measured every 4 hours. Fluid intake, urine output, and electrocardiogram changes were monitored continuously, whereas neurologic assessment was performed every 2 hours. Malnutrition was defined based on weight for age matched for Indian standards.4,6

**Treatment Failure**

The data were reviewed every 4 hours in both groups. Failure to achieve a BG reduction of 18 mg/dL per hour for 2 consecutive hours and/or a decrease or failure to increase in bicarbonate with persistent high anion gap acidosis was considered a nonresponse. A careful review of insulin therapy was performed for errors in dose, preparation, or infusion rate before labeling the nonresponse as treatment failure. The existing infusion rate was thereafter increased by 0.02 U/kg per hour.

**Outcome Measures**

The primary outcome was the rate of decrease in BG until the level reached 250 mg/dL or less. Time to resolution of acidosis, episodes of treatment failures, and incidences of hypokalemia and hypoglycemia were secondary outcomes. Hypokalemia was defined as a serum potassium level less than 3.5 mEq/L and/or suggestive electrocardiographic changes.6 Hypoglycemia was defined as a BG level of 60 mg/dL or less.

**Statistical Analysis**

We estimated sample size to detect noninferiority; low dose was considered noninferior if the difference between the standard and low dose for mean BG decrease did not exceed 18 mg/dL per hour. Previous data suggest that the SD of BG decrease with standard-dose insulin was 24 mg/dL per hour.17 Calculated sample size with a power of 80% using a significance level of .05 (α = .05) was 44. Assuming an attrition rate of 10%, we enrolled 50 participants in total.

Intergroup comparisons were performed using the t test and χ2 test with the Fisher exact test. For assessment of noninferiority, we calculated the differences in BG decrease between the 2 groups with 95% CIs and compared the upper limit of the CI to the preset noninferiority margin. To mitigate the problem of multiple testing for serially measured quantitative outcomes, we used repeated-measures analysis of variance and a summary measure of areas under the curve. To estimate the area under the curve from baseline until 6 hours of insulin therapy, we imputed missing values (few participants in whom target BG values were attained before 6 hours) with multivariate imputation by chained equations.

Hazard ratios (HRs) were estimated for outcomes of BG decrease and resolution of acidosis using Cox proportional model adjusted a priori for age, weight, and acidosis severity. For all secondary outcomes, the Monte Carlo permutation test was performed to adjust for multiple outcomes. For primary outcome, P < .05 was considered statistically significant. Data entry and analysis were performed using IBM-SPSS, version 22 (SPSS Inc), MedCalc, version 13.2 (MedCalc Software), and Stata/IC, version 12 (Stata Corp).

**Results**

**Baseline Characteristics**

Figure 1 shows the trial profile. Of the 57 children screened for eligibility, 50 were enrolled and randomly assigned to the low-dose (n = 25) or standard-dose (n = 25) group. Baseline demographic and biochemical characteristics in both groups were well matched (Table 1). A total of 13 children (26%) were younger than 5 years. New-onset diabetes presenting as DKA was seen in 29 children (58%). A total of 34 children (68%) had severe DKA (pH <7.1 or bicarbonate <5 mEq/L). Twenty-six children (52%) presented with hypoperfusion that required fluid bolus in the first hour. The mean BG decrease after the first hour of fluid therapy was 65 mg/dL (range, 12-190 mg/dL). Incidence of mechanical problems encountered during fluid and insulin infusions were similar in the low- and standard-dose groups (2 vs 4 mechanical problems).

**BG Decrease**

The mean (SD) rate of BG decrease per hour until the level was 250 mg/dL or less was similar in the groups (45.1 [17.6] vs 52.2 [23.4] in the low-dose vs standard-dose group). The difference in mean rates was 7.2 mg/dL per hour (95% CI, −4.7 [favoring low dose] to 19 [favoring standard dose]) mg/dL per hour; the upper limit of the 95% CI just barely surpassing the a priori noninferiority margin of 18 mg/dL per hour (Table 2). The mean
area under the curve values were also similar (AUC, 2201; 95% CI, 2014-2388; vs AUC, 2263; 95% CI, 2093-2434; for low dose vs standard dose; F = 0.47; P = .62).

The serial (hourly) changes in rate of decrease and percentage decrease in BG between the groups revealed no significant difference (F = 0.14; P = .73). However, the mean decrease in BG at the end of first hour of insulin infusion was higher with standard-dose compared with low-dose insulin (61 ± 39 mg/dL) (Table 2). Episodes of BG decrease greater than the desired range (> 90 mg/dL) were also more frequent with the former compared with the latter (12 [10%] of 124 vs 4 [4%] of 113; relative risk, 0.51; 95% CI, 0.21-1.20; P = .05). In fact, no out-of-range decrease was noted with low-dose insulin during the first hour of infusion.

No difference was found in the mean (SD) length of time to achieve a BG level of 250 mg/dL or less between low- and standard-dose groups (6.0 [3.3] vs 6.2 [2.2] hours; P = .80). Seventeen children in the low-dose group and 15 in the standard-dose group attained the BG target (≤ 250 mg/dL) by 6 hours (Figure 2). The HR of achieving a BG level of 250 mg/dL or less by the end of 6 hours was 1.32 times higher in the low-dose group compared with the standard-dose group (adjusted HR, 1.32; 95% CI, 0.64-2.73). However, this difference was not statistically significant (P = .45) (eFigure 1 in the Supplement).

### Resolution of Acidosis
The mean (SD) length of time for resolution of acidosis (end point) was 16.5 (7.2) hours in the low-dose group and 17.2 (7.7) hours in the standard-dose group (P = .73) (Table 3). The rate of resolution of acidosis and serial changes in pH, bicarbonate, and anion gap were all similar (Figure 3). The HR of resolution of acidosis by 24 hours was lower by 22% in the low-dose group compared with the standard-dose group (adjusted HR, 0.78; 95% CI, 0.41-1.47). This difference was not statistically significant (P = .44) (eFigure 2 in the Supplement).

### Therapy-Related Complications
Twelve children (48%) in the standard-dose group compared with 5 (20%) in the low-dose group had at least one episode of hypokalemia (P = .07). This tendency was more pronounced in malnourished children (7 [88%] in the standard-dose group vs 2 [28%] in the low-dose group) (eTable in the Supplement). Episodes of hypoglycemia were also higher with the standard dose, but the difference did not reach statistical significance (5 [20%] vs 2 [8%] in the standard-dose group vs low-dose group; P = .17). More children required measures to counter decreasing BG levels (dextrose increments to ≥ 10%) in the standard-dose group (7 [28%] vs 2 [8%] in the low-dose group) (eTable in the Supplement). Episodes of hypoglycemia were also higher with the standard dose, but the difference did not reach statistical significance (5 [20%] vs 2 [8%] in the standard-dose group vs low-dose group; P = .17). More children required measures to counter decreasing BG levels (dextrose increments to ≥ 10%) in the standard-dose group (7 [28%] vs 2 [8%] in the low-dose group) (eTable in the Supplement). Episodes of hypoglycemia were also higher with the standard dose, but the difference did not reach statistical significance (5 [20%] vs 2 [8%] in the standard-dose group vs low-dose group; P = .17). More children required measures to counter decreasing BG levels (dextrose increments to ≥ 10%) in the standard-dose group (7 [28%] vs 2 [8%] in the low-dose group) (eTable in the Supplement). Episodes of hypoglycemia were also higher with the standard dose, but the difference did not reach statistical significance (5 [20%] vs 2 [8%] in the standard-dose group vs low-dose group; P = .17). More children required measures to counter decreasing BG levels (dextrose increments to ≥ 10%) in the standard-dose group (7 [28%] vs 2 [8%] in the low-dose group) (eTable in the Supplement). Episodes of hypoglycemia were also higher with the standard dose, but the difference did not reach statistical significance (5 [20%] vs 2 [8%] in the standard-dose group vs low-dose group; P = .17). More children required measures to counter decreasing BG levels (dextrose increments to ≥ 10%) in the standard-dose group (7 [28%] vs 2 [8%] in the low-dose group) (eTable in the Supplement). Episodes of hypoglycemia were also higher with the standard dose, but the difference did not reach statistical significance (5 [20%] vs 2 [8%] in the standard-dose group vs low-dose group; P = .17). More children required measures to counter decreasing BG levels (dextrose increments to ≥ 10%) in the standard-dose group (7 [28%] vs 2 [8%] in the low-dose group) (eTable in the Supplement). Episodes of hypoglycemia were also higher with the standard dose, but the difference did not reach statistical significance (5 [20%] vs 2 [8%] in the standard-dose group vs low-dose group; P = .17).

### Discussion
We found that the BG reduction achieved with low-dose insulin was noninferior to that achieved with standard-dose insulin...
lin, although the overall reduction with both regimens remained within the reported range (36-90 mg/dL). The decrease in BG during insulin therapy is the cumulative effect of suppression of hepatic glucose production, stimulation of peripheral glucose uptake, and renal glycosuria, with the first action being the most important.2 However, patients with DKA exhibit some degree of hepatic resistance to insulin action, necessitating higher plasma insulin levels (80-100 μU/mL) to offset this resistance,18 meaning that any effective dose of insulin in DKA should achieve these levels. On the contrary, the currently recommended standard dose of 0.1U/kg per hour has been reported to achieve a plasma insulin concentration much higher than the optimal requisite range (100-200 μU/mL).4,19 This is the justification given in some studies9,10 for lowering the insulin dose to achieve the desired therapeutic response with minimal adverse effects. Although we did not measure plasma insulin levels in this study, our findings extend the above postulate prospectively to show that low-dose insulin achieves a clinically effective BG reduction comparable to standard dose.

Initial hours of DKA management are a matter of concern and controversy. Increasing evidence indicates that fluids and insulin have to be used cautiously in the early hours to prevent a precipitous decrease in BG, rapid electrolyte shifts, and resultant osmotic disequilibrium.10,11 Evidence indicates that higher insulin doses in the first few hours can aggravate a BG decrease but more importantly may lead to rapid changes in electrolytes, thus increasing the risk of cerebral edema.13 Most guidelines, therefore, have eliminated first-hour insulin because hydration alone has been reported to cause a mean BG decrease of 109 mg/dL by improving renal perfusion and clearing osmolar load.11 Our situation is compounded by delayed presentation, missed or delayed diagnosis, and lack of optimum therapy in those diagnosed as having DKA before referral.20 These children tend to be severely acidic and hyperosmolar, thus making the initial hours of therapy more cautious and geared toward prevention of osmotic disequilibrium.14 In light of previously reported observations that confirm that severity of baseline biochemical abnormalities coupled with early insulin and large volumes of fluid increase the risk of cerebral edema,13 our observations on the differences in rate of BG decrease between low and standard doses of insulin in the initial hours could be of interest. We found more episodes of out-of-range (>90 mg/dL) BG decreases with standard-dose insulin. On the contrary, the rate of decrease with low-dose insulin increased gradually every hour until 3 hours to achieve a maximum decrease (54 mg/dL). This finding suggests that the lower dose may be a safer option, particularly in situations in which a gradual decrease in glucose, electrolytes, and resultant osmolality is desired.

We found that low-dose insulin was not inferior to the standard dose in correcting acidosis. The time to resolution of aci-

### Table 2. Primary Outcome Measures (Blood Glucose Decrease)*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Low-Dose Group (n = 25)</th>
<th>Standard-Dose Group (n = 25)</th>
<th>Difference Between Means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood glucose decrease until level is ≤250 mg/dL, mg/dL per hour</td>
<td>45.1 (17.6)</td>
<td>52.2 (23.4)</td>
<td>-7.2 (-19 to 4.7)</td>
</tr>
<tr>
<td>Blood glucose decrease, mg/dL per hour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 h</td>
<td>39.2 (25.5)</td>
<td>61.3 (37.7)</td>
<td>-21.6 (-39.8 to -3.2)</td>
</tr>
<tr>
<td>1-2 h</td>
<td>48.6 (37.7)</td>
<td>39.6 (28.8)</td>
<td>9 (-10 to 28.1)</td>
</tr>
<tr>
<td>2-3 h</td>
<td>54.0 (34.2)</td>
<td>37.7 (32.4)</td>
<td>16.2 (-2.7 to 35.1)</td>
</tr>
<tr>
<td>3-4 h</td>
<td>37.7 (39.6)</td>
<td>41.4 (39.6)</td>
<td>-3.6 (-26.1 to 18.9)</td>
</tr>
<tr>
<td>Blood glucose decrease, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 h</td>
<td>9.3 (6.4)</td>
<td>13.8 (8.3)</td>
<td>-4.5 (-8.71 to -0.28)</td>
</tr>
<tr>
<td>0-2 h</td>
<td>19.3 (10.4)</td>
<td>22.2 (10.9)</td>
<td>-2.9 (-8.95 to 3.15)</td>
</tr>
<tr>
<td>0-3 h</td>
<td>28.4 (10.6)</td>
<td>26.7 (8.8)</td>
<td>1.7 (-3.84 to 7.24)</td>
</tr>
<tr>
<td>0-4 h</td>
<td>33.8 (11.0)</td>
<td>34.6 (13.8)</td>
<td>-0.8 (-7.89 to 6.29)</td>
</tr>
<tr>
<td>Time taken to achieve blood glucose level of ≤250 mg/dL, h</td>
<td>6.0 (3.3)</td>
<td>6.2 (2.2)</td>
<td>0.79 (-1.79 to 1.39)</td>
</tr>
<tr>
<td>Absolute blood glucose decrease until level is ≤250 mg/dL, mg/dL</td>
<td>209 (112)</td>
<td>239 (111)</td>
<td>-30 (-93.41 to 33.41)</td>
</tr>
</tbody>
</table>

* Data are presented as mean (SD).

### Table 3. Secondary Outcome Measures*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Low-Dose Group (n = 25)</th>
<th>Standard-Dose Group (n = 25)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time until resolution of acidosis, mean (SD), h</td>
<td>16.5 (7.2)</td>
<td>17.2 (7.7)</td>
<td>.73</td>
</tr>
<tr>
<td>Children with hypokalemia</td>
<td>5 (20)</td>
<td>12 (48)</td>
<td>.07b</td>
</tr>
<tr>
<td>Children with hypoglycemia</td>
<td>1 (4)</td>
<td>5 (20)</td>
<td>.17b</td>
</tr>
<tr>
<td>Children requiring dextrose concentration ≥10%</td>
<td>2 (8)</td>
<td>7 (28)</td>
<td>.14b</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>2 (8)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>0</td>
<td>1 (4)</td>
<td></td>
</tr>
</tbody>
</table>

* Data are presented as number (percentage) of children unless otherwise indicated.

b P value by Monte Carlo permutation test.
dosis was similar in both, suggesting that the low dose could be as effective as the standard dose in suppressing lipolysis and ketogenesis. Episodes of treatment failures were also rare, and few patients required incremental insulin while on the low-dose regimen. Two studies\(^\text{9,10}\) that compared the 2 insulin regimens have reported similar efficacy in both. Although these studies concur with the findings reported by us, they differ from our study on 2 accounts. Both studies are retrospective and the duration was shorter than the usual described duration of reversal of DKA.

Hypokalemia has remained the most frequent complication of DKA in our setup, with the reported incidence varying from 41% to 82%, much higher than the 4% to 10% reported by our Western counterparts.\(^\text{14,21}\) Underlying malnutrition, poor total body stores of potassium, prolonged illness before presentation, and osmotic diuresis are some of the causal factors for hypokalemia in our patients. In this study too, hypokalemia emerged as the most frequent complication (34%). In addition to these factors, the dose of insulin could have also played a role in lowering serum potassium levels because there was a trend toward a higher proportion of hypokalemia in standard-compared with low-dose insulin. Likewise, hypoglycemia is another important therapy-related complication aggra-

Moulik et al\(^\text{17}\) reported the incidence to be 30.3% with standard-dose insulin, which increased to 64% when malnourished children alone were considered. In the current study, the incidence of hypoglycemia was, however, lower (12%). Although stringent BG monitoring could have contributed to this decreased incidence, the effect of low-dose insulin cannot be completely negated. On the basis of our results, we strongly speculate that low-dose insulin will be a safer option as far as therapy-related complications of DKA are concerned.

Our study has several strengths. First, to the best of our knowledge, this is the first prospective experiment comparing the 2 insulin regimens with a sizeable sample. Second, unlike other studies,\(^\text{9,10}\) our patients have been followed up until the resolution of acidosis. We also have looked at factors unique to developing economies, thus making the applicability of our results more tenable to similar conditions. We believe the limitations associated with an open-label study design were minimized by the objective nature of our study outcomes. However, a few limitations need mention. We could not enroll adolescent children with DKA because our unit cat-

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**Figure 2. Mean Blood Glucose Decrease With Insulin Therapy**

The numbers of children who had not attained a blood glucose level of 250 mg/dL or less at each hour are given in parentheses (\(P = .71, F = 0.47\) for the difference between the 2 groups). To convert blood glucose values to millimoles per liter, multiply by 0.0555. Error bars indicate SD.

**Figure 3. Mean Serial Changes in pH, Bicarbonate, and Anion Gap**

The numbers of children who had not attained end point at each measurement are given in parentheses (\(P = .82, F = 0.36; P = .53, F = 0.77;\) and \(P = .35, F = 1.9\) for the difference between the 2 groups in pH, bicarbonate, and anion gap, respectively). Error bars indicate SD.
gin of 18 mg/dL per hour selected in our trial was possibly stringent. Although the upper limit of the 95% CI for mean difference (19 mg/dL) just exceeded the noninferiority margin, it was less than the entire assumed treatment effect and hence is a statistically persuasive finding. In a clinical context too, an inferior BG decrease when associated with continuing resolution of acidosis is acceptable. Nonetheless, a superiority trial with a larger sample size could possibly have brought out differences in the primary outcome.

Conclusion

Low-dose insulin is noninferior to standard-dose insulin with respect to the rate of BG decrease and resolution of acidosis. Our study opens the door for a subsequent trial with a larger sample size to explore differences in the rate of BG decrease before 0.05 U/kg per hour replaces 0.1 U/kg per hour in the practice recommendations.