

Subcutaneous Use of a Fast-Acting Insulin Analog

An alternative treatment for pediatric patients with diabetic ketoacidosis

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OBJECTIVE — To look for technical simplification and economic efficiency in the treatment of pediatric diabetic ketoacidosis (DKA) with subcutaneous use of the fast-acting insulin analog (lispro) and compare its use with regular intravenous insulin treatment.

RESEARCH DESIGN AND METHODS — In this controlled clinical trial from June 2001 to June 2003, we randomized 60 episodes of DKA with a blood glucose level ≥ 16.6 mmol/l (300 mg/dl), venous pH < 7.3 and/or bicarbonate < 15 mmol/l, or ketonuria greater than $++$. Of the 60 episodes, 30 were treated with subcutaneous lispro (0.15 units/kg) given every 2 h (lispro group) and the other 30 cases received continuous intravenous regular insulin (0.1 unit \cdot kg⁻¹ \cdot h⁻¹; CIRI group). Volume deficit was repaired with 10-ml/kg aliquots of 0.9% sodium chloride. Laboratory monitoring included hourly bedside capillary glucose, venous blood gas, β -hydroxybutyrate, and electrolytes. Plasma blood glucose levels were measured on admission, 2 h after admission, when capillary blood glucose reached ≤ 13.8 mmol/l (250 mg/dl), and 6, 12, and 24 h thereafter.

RESULTS — Capillary glucose levels decreased by 2.9 and 2.6 mmol \cdot l⁻¹ \cdot h⁻¹ in the lispro and CIRI groups, respectively, but blood glucose fluctuated at different time intervals. In the CIRI group, metabolic acidosis and ketosis resolved in the first 6-h period after capillary glucose reached 13.8 mmol/l, whereas in the lispro group, they resolved in the next 6-h interval; however, both groups met DKA recovery criteria without complications.

CONCLUSIONS — DKA treatment with a subcutaneous fast-acting insulin analog represents a cost-effective and technically simplified procedure that precludes intensive care unit admission.

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D iabetic ketoacidosis (DKA) is a life-threatening condition that frequently requires hospitalization in children with type 1 diabetes. The incidence figures for DKA differ (1,2), but DKA still stands as the most common cause of diabetes-related death in chil-

dren (1,3). The critical factors in the treatment of DKA include careful and frequent monitoring of the patient, skillful fluid and electrolyte adjustment, and the initiation of insulin therapy after the initial restoration of fluid volume has been achieved. Many reports have indi-

cated that low-dose insulin therapy is quite effective regardless of the route of administration, whether intravenous, intramuscular, or subcutaneous (4–9). Continuous low-dosage intravenous infusion of soluble insulin has been the procedure of choice outlined in pediatric management guidelines because it provides direct control and results in a predictable rate of fall in serum glucose levels (1,10–13). However, admission to an intensive care unit to receive intravenous insulin infusion increases health care costs (14–17).

To avoid the need for a second intravenous line, simplify treatment of DKA, and provide a more economical solution, we proposed using a subcutaneous fast-acting analog of human insulin instead of intravenous continuous regular insulin. The aim of our study was to compare the efficacy of a subcutaneous fast-acting analog (lispro) with continuous intravenous regular insulin (CIRI) in the treatment of pediatric DKA.

RESEARCH DESIGN AND METHODS

We studied 60 DKA occurrences in children admitted to the emergency department of the São Paulo University Children's Hospital from June 2001 to June 2003, in which blood glucose levels were ≥ 16.6 mmol/l (300 mg/dl), pH was < 7.3 and/or serum bicarbonate was < 15 mmol/l, and ketonuria was greater than $++$, independent of mental status. Patients requiring surgical procedures or under treatment with glucocorticoid or immunosuppressive agents were excluded from the study. The local ethics investigation committee approved the protocol, and informed consent was obtained from family members.

Of the 60 DKA episodes, 30 were randomized to treatment with a subcutaneous fast-acting insulin analog (lispro) and the other 30 were randomized to treatment with CIRI (Fig. 1).

The lispro group included 25 children and adolescents (8 boys, 17 girls; median age 11.3 years, range 3–17 years)

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Abbreviations: CIRI, continuous intravenous regular insulin; DKA, diabetic ketoacidosis.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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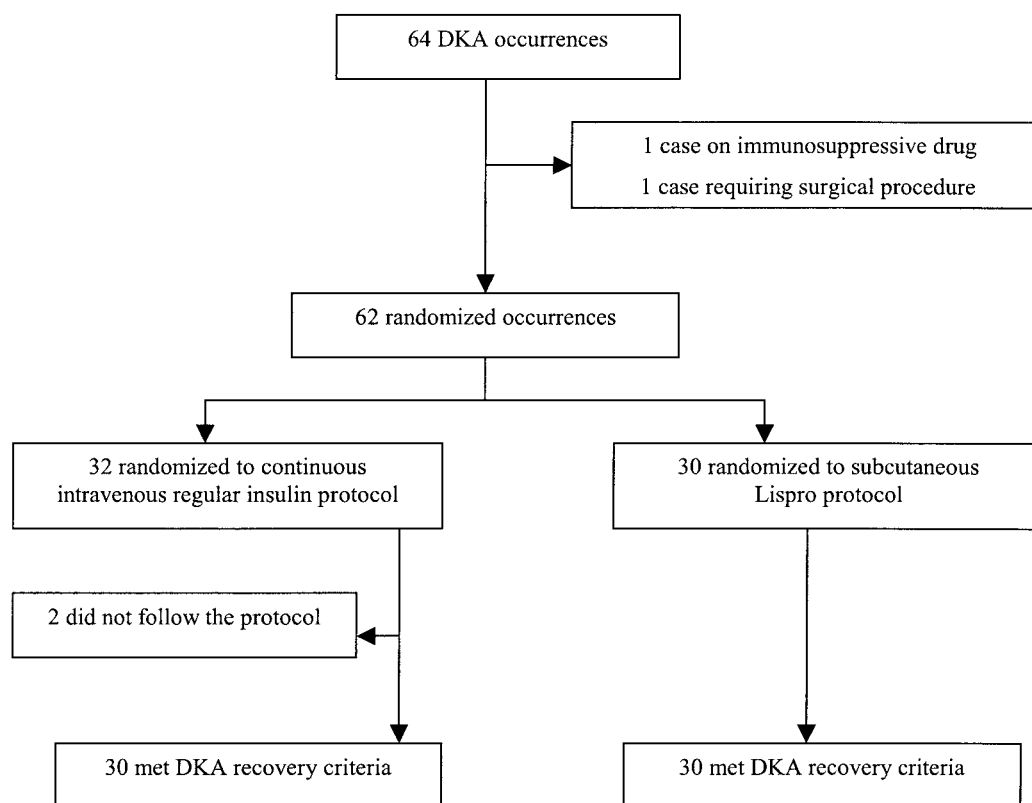


Figure 1—Trial profile.

and the CIRI group included 21 patients (5 boys, 16 girls; mean age 12.1 years, range 5.5–18 years).

The causes of diabetic ketoacidosis in the lispro and CIRI groups were, respectively, new-onset diabetes (6 vs. 5 cases), infection (8 vs. 4 cases), excessive food intake (13 vs. 13 cases), missed injection (10 vs. 5 cases), and unidentified causes (1 vs. 4 cases). The laboratory characteristics at admission in the lispro and CIRI groups were, respectively, a mean blood glucose concentration of 24.6 ± 7.9 vs. 24.6 ± 8.1 mmol/l, a mean serum bicarbonate of 10.38 ± 4.74 vs. 9.08 ± 3.61 mmol/l, and a pH of 7.17 ± 0.10 vs. 7.18 ± 0.10 . Both groups presented with anion gap metabolic acidosis (22.35 ± 7.23 vs. 29.55 ± 9.04 mmol/l) with an elevated serum β -hydroxybutyrate concentration (8.16 ± 3.53 vs. 8.45 ± 2.75 mmol/l). Electrolyte characteristics on admission are shown in Table 1. Patients were determined to have recovered from the DKA episode once they met clinical criteria (i.e., were mentally alert and able to eat) and biochemical criteria (i.e., venous pH >7.3 , serum bicarbonate >15 mmol/l, and anion gap <16 mmol/l).

Fluid protocol

In the emergency room, a catheter was inserted into an antecubital vein for blood sampling and fluid replacement. Normal saline (0.9% NaCl) was infused at the rate of $20 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ to restore peripheral perfusion. After the 2nd h, the infusion rate of normal saline was decreased to $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ until volume reparation was achieved. Potassium (20 mEq/l) was

added to normal saline to maintain serum potassium concentrations at >3.8 mmol/l as soon as urine was produced and a serum potassium level <6.5 mmol/l was confirmed. Bicarbonate replacement ($1 \text{ mmol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) was given if venous pH was <7.0 or serum bicarbonate was <5 mmol/l, and phosphate was supplemented only if its serum level was <0.5 mmol/l. If the patient was unable to eat

Table 1—Patient characteristics and initial serum biochemical values

	Lispro group	CIRI group
Age (years)	11.3 ± 3.6	12.1 ± 3.3
Weight (kg)	39.06 ± 12.86	41.6 ± 12.2
Male/Female	8/17	5/16
pH	7.17 ± 0.10	7.18 ± 0.10
Anion gap (mmol/l)	22.35 ± 7.23	29.55 ± 9.04
β -Hydroxybutyrate (mmol/l)	8.16 ± 3.53	8.45 ± 2.75
Glucose (mmol/l)	24.6 ± 7.9	24.6 ± 8.1
Na^+ (mmol/l)	137.09 ± 4.79	136.68 ± 4.09
K^+ (mmol/l)	5.11 ± 0.61	5.08 ± 0.77
Cl^- (mmol/l)	109.86 ± 6.56	105.13 ± 9.37
HCO_3^- (mmol/l)	10.38 ± 4.47	9.08 ± 3.61
Serum osmolality (mOsm/kg)	311.95 ± 13.71	312.91 ± 13.81

Data are means \pm SD.

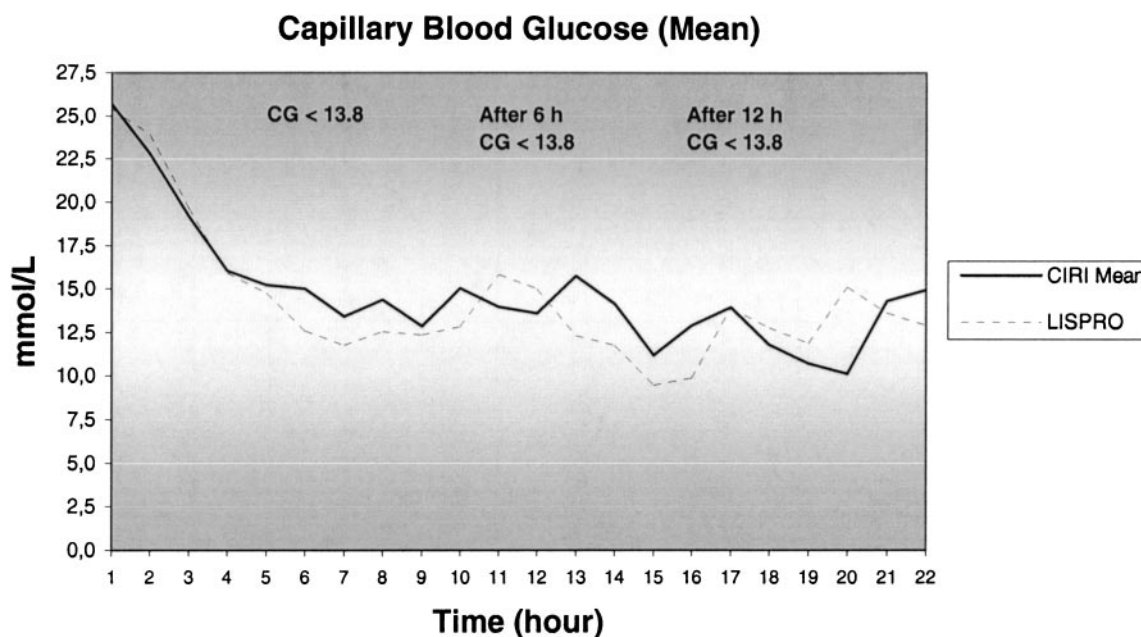


Figure 2—Mean capillary glucose (CG) in lispro and CIRI groups during DKA treatment.

when the capillary blood glucose concentration reached 13.8 mmol/l (250 mg/dl), glucose (5 g/dl) was added to the fluid regimen.

Insulin therapy

Insulin therapy was initiated ~1–2 h from the time rehydration began. In the lispro group, 0.15 units/kg of a fast-acting insulin analog was administered subcutaneously every 2 h, according to the results of capillary blood glucose determinations by fingerstick; when capillary blood glucose levels neared 13.8 mmol/l, 0.15 units/kg lispro insulin were administered every 4 h for the next 24 h. In the control (CIRI) group, regular insulin was infused with a syringe pump (Nikkiso) at a rate of $0.1 \text{ unit} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ from an independent intravenous line through a second catheter inserted into a peripheral vein. Capillary blood glucose levels were taken hourly. This infusion was continued until capillary blood glucose levels decreased to $\leq 13.8 \text{ mmol/l}$; thereafter, 0.15 units/kg regular insulin were given subcutaneously 30 min before stopping the intravenous line and every 4 h for the next 24 h. After ~12 h of intensive fast-acting insulin administration, intermediate human insulin was initiated at a dosage of 0.4 unit/kg every 12 h in both groups.

Laboratory monitoring included hourly bedside meter blood glucose determinations (Advantage; Roche). In ad-

dition, venous blood gas (CIBA-Corning 278/280), β -hydroxybutyrate (Ranbut; Randox, Crumlin, U.K.), electrolytes (ion-selective electrode), plasma blood glucose (ultraviolet hexokinase; Wiener, Rosario, Argentina), phosphate, magnesium (colorimetric), urea nitrogen (UV GIDH-SMT; Merck, Darmstadt, Germany), and creatinine (colorimetric, kinetic) levels were measured on admission, 2 h after admission, at the time capillary blood glucose reached 13.8 mmol/l, and 6, 12, and 24 h thereafter. Urine ketones were monitored in all voids (Bayer strips).

Statistical analysis

Because biochemical data were not continuously measured, differences in profiles between the lispro and CIRI groups were evaluated each time using an unpaired Student's *t* test, with the exception of venous pH, which was evaluated using the Mann-Whitney *U* test. All data were analyzed using the Statistical Package for Social Sciences (SPSS 9.0.1), with $P < 0.05$ taken as statistically significant.

RESULTS— Of the 60 DKA episodes, 57 were treated in the emergency department and 3 were treated in the intensive care unit. Fluid replacement was based on clinical assessment of the deficit, and a mean volume of $44 \pm 17.9 \text{ ml/kg}$ of normal saline was administered during a mean period of $4.4 \pm 2.3 \text{ h}$ in the lispro

group, whereas $42.7 \pm 17.4 \text{ ml/kg}$ of normal saline was given to the CIRI group over a $4.5 \pm 2.2\text{-h}$ period.

Capillary glucose level was the only variable continuously measured (hourly), whereas other variables were taken in predefined moments after glucose levels reached 13.8 mmol/l. Figure 2 depicts the mean capillary glucose levels after admission. In both groups, ~6 h were required to reach the capillary glucose concentration of 13.8 mmol/l. There were 10 mild hypoglycemic episodes ($< 3.3 \text{ mmol/l}$) during DKA management (CIRI, $n = 6$; lispro, $n = 4$).

In the lispro group, the mean decrease in capillary glucose was $2.9 \text{ mmol} \cdot \text{l}^{-1} \cdot \text{h}^{-1}$, with a mean insulin dose of $0.28 \pm 0.19 \text{ units/kg}$, whereas in the CIRI group, capillary glucose fell $2.6 \text{ mmol} \cdot \text{l}^{-1} \cdot \text{h}^{-1}$ with a mean insulin dose of $0.37 \pm 0.24 \text{ units/kg}$. The mean blood glucose concentration 6 h after capillary glucose reached 13.8 mmol/l was lower in the CIRI than in the lispro group (10.4 ± 4.8 vs. $13.4 \pm 4.6 \text{ mmol/l}$; $P < 0.05$); however, the levels fluctuated at different time intervals. Table 2 shows the mean values of the variables studied.

In the CIRI group, metabolic acidosis ($\text{pH} > 7.3$, bicarbonate $> 15 \text{ mmol/l}$, and anion gap $< 16 \text{ mmol/l}$) (18) and ketosis (β -hydroxybutyrate $< 3 \text{ mmol/l}$) resolved 6 h after capillary glucose reached $\leq 13.8 \text{ mmol/l}$; in the lispro group, they resolved

Table 2—Biochemical characteristics of lispro and CIRI groups during DKA treatment

	Blood glucose (mmol/l)	pH	HCO ₃ ⁻ (mmol/l)	β-Hydroxybutyrate (mmol/l)	Anion gap (mmol/l)	Serum osmolality (mOsm/kg)
Initial						
CIRI	24.6 ± 8.1	7.18 ± 0.1	9.08 ± 3.61	8.45 ± 2.75	29.55	312.91 ± 13.81
Lispro	24.6 ± 7.9	7.17 ± 0.1	10.38 ± 4.74	8.16 ± 3.53	22.35	311.95 ± 13.71
After 2 h						
CIRI	18.5 ± 4.1	7.19 ± 0.11	9.76 ± 4.08	7.08 ± 2.56	25.47	310.91 ± 12.36
Lispro	18.6 ± 7.0	7.15 ± 0.13	9.83 ± 5.71	7.54 ± 3.53	25.1	305.77 ± 16.18
At CG ≤ 13.8 mmol/l						
CIRI	12.4 ± 2.3	7.24 ± 0.12	9.76 ± 4.08	4.08 ± 2.58	19.3	305.37 ± 13.68
Lispro	11.9 ± 3.7	7.22 ± 0.12	9.83 ± 5.71	5.18 ± 3.17	17.68	302.25 ± 13.26
6 h after CG ≤ 13.8 mmol/l						
CIRI	10.4 ± 4.8*	7.31 ± 0.09	15.79 ± 4.42	2.61 ± 2.18	14.55	297.61 ± 11.16
Lispro	13.4 ± 4.6	7.29 ± 0.08	14.25 ± 6.10	3.29 ± 2.84	17.2	296.54 ± 10.34
12 h after CG ≤ 13.8 mmol/l						
CIRI	13.4 ± 6.8	7.36 ± 0.04*	18.39 ± 3.66	1.57 ± 1.82	16.02	297.61 ± 11.16
Lispro	11.7 ± 5.6	7.31 ± 0.05	16.78 ± 6.27	2.0 ± 2.0	14.12	296.54 ± 10.34
24 h after CG ≤ 13.8 mmol/l						
CIRI	15.0 ± 7.4	7.37 ± 0.07	19.52 ± 5.10	0.84 ± 0.91	13.51	302.36 ± 10.06
Lispro	13.7 ± 5.1	7.37 ± 0.06	18.19 ± 4.72	1.12 ± 1.59	14.5	297.22 ± 5.37

Data are means ± SD. CG, capillary glucose. * $P < 0.05$.

in the next 6-h interval. Alkali therapy was used in 10 patients (CIRI, $n = 4$; lispro, $n = 6$).

The mean serum levels of Na, corrected Na, urea nitrogen, creatinine, and magnesium were in the normal range during the whole treatment. Potassium concentrations decreased as the pH increased, in both groups, 24 h after capillary glucose reached 13.8 mmol/l (3.68 ± 0.55 vs. 4.05 ± 0.44 mmol/l; $P < 0.05$), especially in the CIRI group.

A discrete hyperchloremia was noticed in both groups, but it was self-limited. Phosphate levels fell continuously but rarely reached the level for replacement (<0.5 mmol/l). Serum osmolality was not normalized in either group. Although metabolic homeostasis was not restored within 30 h of treatment, the patients were alert and able to tolerate oral food intake (15).

There were no deaths or "near death" episodes (19,20) or cases of cerebral edema, and no patient had to be treated with mannitol.

CONCLUSIONS— The most frequent reason for DKA in our patients was poor compliance with their insulin regimen, especially the adolescent girls. Most of the DKA episodes were treated in the emergency department ($n = 57$) of our institution for 2–3 days, until severe hy-

perglycemia and acid-base disturbances were resolved; patients were frequently sent home directly from the emergency department unless some complication (e.g., infection) required them to complete their treatment in our pediatric ward. We recognize that admitting patients into intensive care units is difficult in most public hospitals in developing countries where the beds are usually occupied by children requiring ventilator support.

Our fluid replacement protocol aimed at correcting intravascular volume up to the normalization of the peripheral perfusion. Once cardiovascular stability was achieved, the child was alert, and vomiting has stopped, oral rehydration was started. When oral feeding was not possible, maintenance intravenous fluids were added.

It has been suggested that cerebral edema takes place during the recovery phase of DKA and may be related to the fall of extracellular osmolality (1,21,22). In this sense, the use of hypo-osmolar fluids, such as 0.45% NaCl, could be a factor in worsening the condition, whereas the use of normal saline could play a protective role (23,24). In support of this idea, our patients' Na (corrected by Katz formula) (14) was maintained in the normal range during the whole period of treatment in both groups and we did not have

to administer hypotonic fluid at any time. On the other hand, potassium administration, begun in the 2nd h of treatment because of serum concentrations <6.5 mmol/l, was efficient, and no patient experienced hypo- or hyperkalemia. Although there was a fall in the potassium levels concomitant with the rise in venous pH, the mean serum potassium levels were kept at >3.5 mmol/l (25) at all times.

Many studies have demonstrated that low doses of insulin, sufficient to allow a glycemic fall between 2.8 and 5.6 mmol \cdot l⁻¹ \cdot h⁻¹ regardless of the administration route, are able to suppress lipolysis and ketone production and yet improve peripheral glucose utilization (6–9,26). This level of insulin minimizes the risk of hypokalemia, hypoglycemia, and an abrupt fall in serum osmolality.

It took 6 h for both groups to reach a capillary glucose concentration <13.8 mmol/l, which shows that the 2-h interval between the lispro shots was effective. However, when we spaced the shots to every 4 h, the glycemic control worsened, indicating that this was a too long a time to maintain the insulin analog action. Metabolic acidosis and ketosis resolved earlier in the CIRI than in the lispro group, probably reflecting a less-than-optimum 4-h lispro schedule. We speculate that when capillary glucose levels

reached 13.8 mmol/l, continuing subcutaneous lispro injections at a lower dose and shorter time interval may have been a better option. Umpierrez et al. (27) recently observed comparable blood glucose decrease rates and times for ketoacidosis control between groups of adults receiving subcutaneous aspart insulin every 1–2 h and a group treated with intravenous regular insulin.

DKA recovery criteria were met 12 h after capillary glucose reached 13.8 mmol/l. At no time during treatment were there any differences in β -hydroxybutyric acid between both groups, which shows the effectiveness of subcutaneous insulin analogs in the treatment of DKA. A short-lasting hyperchloremia was noticed in both groups. Because we used KCl and NaCl, the chloride load could have increased serum levels and eventually worsened the metabolic acidosis; however, as normal perfusion was restored, the renal chloride excretion normalized the serum levels.

One of the most controversial aspects of DKA treatment is the administration of sodium bicarbonate. The disadvantages are manifold and include increased risk of hypokalemia, reduced oxygen delivery to the tissues, and decreased cerebrospinal fluid pH. We give bicarbonate only in situations where the acidosis is so intense (pH < 7.0 and bicarbonate < 5.0 mmol/l) that it is, in itself, life threatening because at this stage of very low alkali reserve, any increase in the acid load could lead to a fatal acidosis (25). In 10 patients, we needed to administer bicarbonate (CIRI, $n = 4$; lispro, $n = 6$) in the first 2 h of treatment.

Although phosphate levels decreased during treatment, it did not drop to < 0.5 mmol/l in any patient.

Cerebral edema, the most feared complication of DKA, did not develop in our patients. It affects mainly children and adolescents (0.46–4.6%) and has a high mortality rate (up to 25%), and sequelae occur in 10–25% of survivors (1). Many factors have been implicated in cerebral edema, such as the degree of acidosis and hyperglycemia, changes in serum osmolality and oncotic pressure, hypernatremia at admission, low $p\text{CO}_2$, use of bicarbonate, and vigorous fluid infusion, especially in the first hours of treatment, leading to a sharp fall in glycemic levels (21–24). However, there is no consensus that hypotonic fluids predispose a patient

to cerebral edema. Adrogue et al. (28), Harris and Fiordolisi (19), and Inward and Chambers (20) have observed that the administration of small fluid volumes blocks the decompensation process without creating conditions for central nervous system complications. None of our patients had cerebral edema, and it is noteworthy that even after 30 h of treatment, all of them had a slight degree of hyperosmolality.

In our institution, patients with DKA are often managed in the emergency department due to restrictions on supervision and nursing care in general wards. We believe that the most important tenets of DKA treatment are frequent monitoring of the patient and a skillful fluid replacement, regardless of the setting in which the patient is treated.

The international consensus statement on DKA in children and adolescents (1) indicates that low-dose intravenous insulin administration should be the standard of care. As pointed out recently by Umpierrez et al. (17), we agree that protocols of DKA treatment with subcutaneous rapid-acting analogs represent a technical simplification and may lower the mean cost for hospitalization as a patient would not need either infusion pumps or a second intravenous line. Our protocol of subcutaneous injections every 2 h until capillary glucose levels neared 13.8 mmol/l and every 4 h thereafter was very well accepted by the emergency department staff.

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