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ORIGINAL ARTICLE

Implementation of a Clinical Practice Guideline for diabetic ketoacidosis at a tertiary pediatric hospital: a before-after study

Implementación de una Guía de Práctica Clínica de cetoacidosis diabética en un hospital pediátrico de tercer nivel. Estudio antes-después

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What do we know about the subject matter of this study?

Type 1 diabetes is common in pediatrics, and its most frequent serious complication is diabetic ketoacidosis (DKA). Clinical practice guidelines (CPGs) reduce hospital stays, improve emergency room efficiency, and reduce risk factors for developing cerebral edema. The International Society for Pediatric and Adolescent Diabetes (ISPAD) supports their use.

What does this study contribute to what is already known?

This study shows the impact of implementing a CPG in the management of DKA in children. It highlights how its application reduces risk factors associated with treatment and linked to the development of cerebral edema. It reinforces the importance of CPGs in improving the quality and safety of care, as well as their value as a tool for updating and adjusting good practices.

Abstract

Diabetic ketoacidosis (DKA) is the leading cause of morbidity and mortality in pediatric diabetes, mainly due to cerebral edema (CE). Standardized treatment reduces the risk of CE. **Objective**: To compare the duration of DKA episodes and risk factors for CE after implementing clinical practice guidelines (CPGs). **Patients and Method:** A before-and-after study was conducted in children aged < 18 years with DKA admitted to the Emergency Department between 01/01/2017-12/31/2018 (PRE-CPG) and 01/01/2021-12/31/2022 (CPG). Patients with comorbidities were excluded. Demographic, clinical, laboratory, and treatment variables were recorded, as well as DKA episode duration and CE risk factors (early insulin administration within the first hour and use of bicarbonate for correction). Survival analysis and Cox proportional hazards modeling were performed, reporting hazard ratios (HR) and 95% confidence intervals (95% CI). **Results:** A total of 76 children in PRE-CPG and 71 in CPG were included. The CPG group showed a higher proportion of diabetic onset (70% vs. 34%,

Keywords:
Diabetic Ketoacidosis;
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p < 0.01). Episode duration was longer in the CPG group than the PRE-CPG one (14 h [IQR 9.5-20] vs. 9.8 h [IQR 5.3-12.5]; p = 0.01, respectively). The resolution curve was faster in the PRE-CPG group (HR 0.62; 95% CI 0.43-0.90; p = 0.017). Compared with the PRE-CPG group, the CPG one showed lower insulin administration in the first hour (7% vs. 57%, p < 0.01) and lower bicarbonate use (1% vs. 8%, p = 0.037). **Conclusions:** The implementation of the CPG was associated with longer DKA episodes and a reduction in treatment-related CE risk factors, such as early insulin administration and bicarbonate use.

Introduction

Worldwide, type 1 diabetes (T1D) is one of the most common chronic diseases in children and adolescents and has a variable incidence depending on the region and ethnicity, with an increase in recent years. Diabetic ketoacidosis (DKA) is the most commonly observed hyperglycemic emergency in children with T1D. It is caused by an absolute or relative insulin deficiency and an increase in counter-regulatory hormones (growth hormone, cortisol, and glucagon), which lead to the classic triad of hyperglycemia, metabolic acidosis, and volume depletion. It is the leading cause of morbidity and mortality in children and adolescents with T1D and constitutes a frequent reason for presentation to pediatric emergency departments (PEDs)[1-3].

Our institution manages approximately 40 episodes per year (Conditions for admission and therapeutic approach for children with DKA in an emergency department; paper presented at the 9th Congress of Emergencyand Critical Care; Argentine Society of Pediatrics, 2020). Between 30-80% of diabetic onset manifests as DKA[3] . Timely diagnosis and appropriate management are crucial to minimizecomplications, especially cerebral edema (CE)[4]. DKA mortality is mainly due to the development of CE, which is related to both the severity of the episode and treatment[5-8].

Treatment-related risk factors include initiation of insulin therapy withinthe first hour of treatment, correction with intravenous sodium bicarbonate (Bic), administration of inappropriate intravenous sodium concentrations, and infusion of excessive fluid volumes in the first 4 hours of treatment[5-8]. The implementation of clinical practice guidelines (CPGs) has been shown to reduce PED length of stay and optimize resource utilization[9-11]. In its latest publication, the ISPAD emphasizes the use of written or web-based CPGs as the foundation of DKA management[12]. In 2019, our group conducted a study assessingthe incidence of risk factors for the development of DKA in a cohort of patients with DKA, revealing a high proportion of insulin administration before the first treatment hour and several instances of Bic correction in severe DKA(Conditions for admission and therapeutic approach for children with DKA in an emergency department; paper presented at the 9th Congress of Emergencies and Critical Care; Argentine Society of Pediatrics, 2020). The management of the condition in that study was based on the guidelines published in 2000[13] and on an update published in an internal medicine manual (Internal Medicine Course at Garrahan Hospital [MIP], 4th year, Diabetic Ketoacidosis, p. 45.70). In July 2020, the first DKA CPG adapted to our center was published, using the GRADE approach (Krochik G, Zuazaga M, Fustiñana A, Carolina, Mateu C, Prieto M, et al. GAP 2020 Management of Diabetic Ketoacidosis in Pediatrics. 2020;1-35. Available at www.garrahan.gov.ar) (supplementary table 1, available online).

The objective of this study is to compare the duration of the DKA episode until resolution and the frequency the frequency of CE-related risk factors and treatment-associated complications following the implementation of an institutionally adapted CPG (CPG group) versus the pre-implementation period (PRE-CPG group).

Patients and Method

Retrospective before-and-after study. medical records of all patients aged 1 month to 18 years who were admitted to the PED of our institution with a diagnosis of DKA during two periods were reviewed. The first period was from January 1, 2017, to December 31, 2018, prior to the implementation of the DKA CPG (PRE-CPG group), and the second period extendedfrom January 1, 2021, to December 31, 2022, following the introduction of the CPG(CPG group). Patients were included if they met the DKA criteria established by the ISPAD:: 1) blood glucose > 200 mg/dl, and 2) ketonuria ≥ 2 + and/or blood ketones > 3 mmol/l; and 3) HCO_3 < 15 mEq/l and/or pH < 7.30. Patients with significant comorbidities (hematological-oncological diseases, solid organ transplants, cardiomyopathies, cystic fibrosis, prolonged treatment with corticosteroids) were excluded, except for those withceliac disease, thyroid disorders, or diabetes-associated autoimmune disorders. Mixed hyperglyce-

mic states were also excluded, such as DKA combined with hyperosmolar state (blood glucose > 600 mg/dl, effective serum osmolality ≥ 320 mOsm/kg, hypovolemia, pH > 7.3, and HCO_3 > 15 mEq/l, absence or mild ketonemia and mild ketonuria, and consciousness alterations)[14].

The study was conducted at a terciary care pediatric hospital, where care in the PED is provided by specialists in pediatric emergency medicine from 8 a.m. to 8 p.m. on weekdays and by general pediatricians during night shifts and weekends. The hospital attends approximately 120,000 consultations anually, with around 14000 hospital admissions per year. The Nutrition Service includes physicians specialized in diabetes management.

Demographic, clinical, and laboratory variables were recorded upon admission (pH, pCO_2, Bic, urea, potassium, sodium, phosphate). Treatment- related variables were also recorded, including:volume and type of fluids administered in the first hour, total fluids administered during the first 4 hours and throughout the episode (ml/m^2), and sodium concentration in maintenance fluid. The severity of the DKA episode was classified according to the admission laboratory values as follows: mild: pH < 7.30 and/or Bic < 15 mEq/L; 2) moderate: pH < 7.20 and/or Bic < 10 mEq/L; and 3) severe: pH < 7.10 and/or Bic < 5 mEq/L[14].

Outcome measures included:admission to the intensive care unit (ICU), development of CE, COVID-19 infection (detected by antigen or positive PCR), and death. Adherence to the CPG was defined when both of the following criteria were met:: 1) patients received the initial and maintenance fluids as recommended by the CPG according on DKA severity; 2) sodium concentration in maintenance was prescribed according to the corrected serum sodium value from the first laboratory test, as suggested by the CPG. The primary outcome of the study was the duration of the episode, defined as the time(in hours) from admission to resolution

(pH > 7.3 and Bic ≥ 15 mEq/L and ketonemia < 1 mmol/L or trace amounts of ketones in urine).

Risk factors for CE were categorized as:: *non-modifiable* (age < 5 years, DKA at disease onset, urea

> 40 mg/dL upon admission , pCO_2 ≤ 21 mmHg) and *modifiable* (initiation of insulin therapy within the first treatment hour, correction with intravenous Bic, corrected sodium decrease > 2 mEq/L/h, and fluid volume > 50 mL/kg in the first 4 hours of treatment). Additional variables included rapid variationsin blood glucose (> 100 mg/dL per hour) or hypoglycemia (blood glucose < 54 mg/dL) were also recorded. CE was considered present when either the diagnosis was recorded in the medical history or specific treatment (mannitol or hypertonic saline) was indicated.

Statistical analysis

Frequencies and percentages were used to describe categorical variables, and medians and interquartile ranges (IQR) for continuous variables. Comparisons between groups were performed using the chi- square test for categorical variables and the Mann-Whitney U test for continuous variables. A survival analysis was performed to compare DKA episode duration between groups,. The log-rank test was reported. A Cox regression model was also performed to adjust for all variables that we considered biologically important and those that had a p ≤ 0.2 in the univariate analysis. Results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). Statistical significance was set at p < 0.05.

Data were collected using a REDcap® electronic database, and analyses were performed with SPSS v.24 and Stata v.14 sofware

The study protocol was approved by the Research and Ethics Committee of our institution, *Hospital Pediátrico Prof. Dr. Juan Pedro Garrahan*.

Results

76 children were included in the PRE CPG group and 79 in the CPG group. Of the CPG group, 90% adhered to the guidelines, leaving 71 patients in this group for analysis. Children in the CPG group were younger (median age 9.8 years [IQR 5.3-12.5] vs. 12.7 years [IQR 9.3-14.1]; p = 0.01) and had a higher proportion of new-onset diabetes episodes(70% vs. 34%; p < 0.01) (Table 1). This group also presented with higher blood glucose levels (504 mg/dL [IQR 400-623] vs. 454 mg/dL [IQR 354-556]; p = 0.047) and lower urea levels (27 mg/dl [IQR 20-36] vs. 33 mg/dl [IQR 23-45]; p = 0.06) at admission.

Table 2 describes treatment and clinical evolution. The CPG group showed a higher rate of ICU admissions (11% vs. 8%; p = 0.48), although the difference was not statiscally significant. Two cases of COVID-19 infection were recorded in the CPG group. The duration of the DKA episodes (Table 2) was longer in the CPG group, with a median of 14 hours (IQR 9.4-18.5) compared to 10.5 hours (IQR 8-14) for the PRE CPG group (p = 0.01). Figure 1 shows the kaplan-Meier curves for DKA resolution time, indicating faster resolution in the PRE-CPG group (log-rank test p < 0.01).

No significant differences were observed of hypoglycemia or hypokalemiabetween groups in the frequency of hypoglycemia and hypokalemia (Table 2). Although the difference in hypophosphatemia at admission was not statistically significant (phosphate < 2 mEq/L: 5.6% PRE CPG vs. 3.8% CPG; p = 0.6), the

CPG group showed a greater need for phosphate replacement during treatment.. No cases of CE were reported. Table 3 summarizes the risk factors for CE. Among patient- related factors, the CPG group included , a higher proportion of children < 5 years of age (20% vs. 11%; p < 0.01) and more new onset diabetes episodes (70% vs. 34%; p < 0.01), as well as fewer patients with urea > 40 mg/dl (11% vs. 34%; p = 0.01). Regarding treatment- related risk factors, the CPG group demonstrated a marked decrease in the initiation of insulin therapy during the first treatment hour (3% vs. 57%; p < 0.01) and in the indication for Bic correction (1% vs. 8%; p = 0.046)

Table 4 describes the multivariate Cox regression model, adjusted for age, pH, urea, blood glucose, and new onset diabetes. The analysis revealed a significantly higher likelihood of DKA resolution in the PRE-CPG group, (HR 0.62 [95% CI 0.43-0.90]; p = 0.017). No deaths were recorded in either group.

Discussion

Our study shows that implementing a protocolized treatment for DKA reduces treatment-related risk factors for CE without increasing the frequency of associated complications. In our

Cohort , after the implementation of the CPG, there was a marked reduction in the rate of insulin administration during the first treatment hour and in the use of intravenous bicarbonate correction among children with severe DKA, two of the main modifiable risk factor for CE[5,6]. Although the study design does not allow us to directly asses the reduction of CE incidence, it could be inferred that decreasing these risk factors could contribute to lowering its ocurrence.

Despite the improvements in management practices, we observed, that the duration of DKA episodes was longer following the implementation of the CPG. A possible explanation for this finding may relate to the lower fluid volumes recommended in the updated guideline compared with previous management approaches (Supplementary Table 1, available online). Another possible explanation could be the continuation administration of high intravenous glucose concentrations after DKA resolution, , while awaiting the initiation of basal insulin therapy.

Having standardizard clinical care guidelines not only ensures that practise aligns with the best available evidence but also promotes quality and safety in patient care. Moreover, CPGs help identify areas with limited evidence, encourages new research, and foster continuous improvement in best practices.. The results obtained suggest the need to review the protocolized indications and conduct further evaluations on the impact of these modifications.

Significant differences were observed between the PRE CPG and CPG groups. The frequency of new-onset T1D presenting with DKA nealy doubled in th CPG group, accompanied by an increased requirement for

Table 1. Descriptive, clinical, and laboratory characteristics at admission of patients with diabetic ketoacidosis according to the use of clinical practice guidelines (n = 147)

	Total n=147	Pre-CPG n=76	CPG n=71	p
Age (years), median (IQR)	11,6 (7,2-13,5)	12,7 (9,3-14,1)	9,8 (5,3-12,5)	0,01*
Female sex, n (%)	77 (52)	40 (53)	37 (52)	0,95
New-onset diabetes, n (%)	76 (52)	26 (34)	50 (70)	< 0,01*
Severity of the episode				0,86
Mild, n (%)	42 (29)	23 (30)	19 (27)	
Moderate, n (%)	48 (33)	25 (33)	23 (32)	
Severe, n (%))	57 (39)	28 (37)	29 (41)	
Admission laboratory				
Glucose (mg/dL), median (IQR)	478 (375-602)	454 (354-556)	504 (400-629)	0,047*
pH, median (IQR)	7,14(7,06-7,23)	7,15 (7,06-7,24)	7,13 (7,06-7,23)	0,68
Sodium bicarbonate (mEq/L), median (IQR)	8,4 (6-11,8)	9,6 (6,8-11,9)	8 (5,3-11,8)	0,2
Urea (mg/dL), median (IQR)	31 (21-40)	33 (23-45)	27 (20-36)	0,06
Potassium (mEq/L), median (IQR)	4,4 (3,8- 4,9)	4,5 (4,1-4,9)	4,3 (3,7-4,6)	0,007*
Sodium (mEq/L), median (IQR)	135 (132-138)	135 (132-137)	135 (133-138)	0,54
Phosphate (mEq/L), median (IQR)	3,9 (3,3-5,2)	4,1 (3,4-5,6)	3,8 (3,2-5,1)	0,15

Pre-CPG = group before implementation of Clinical Practice Guidelines; CPG = group after implementation of Clinical Practice Guidelines.

Table 2. Comparison of treatment, clinical course, and complications in children with DKA during both periods

	Pre-CPG n = 76	CPG n = 71	p
Fluids and electrolytes administered			
Maintenance fluids (mL/m²/day), median (IQR)	3.350 (3.000-4.000)	3.000 (3.000-3.500)	0,09
Na^+ concentration in maintenance fluids (mEq/L), median (IQR)	100 (88-100)	100 (100-100)	< 0,01*
Fluid in the first 4 hours (mL/kg), median (IQR)	23 (19-28)	28 (23-35)	< 0,01*
DKA duration (h), median (IQR)	10,5 (8-14)	14 (9,4-18,5)	0,01*
ICU requirement, n (%)	6 (8)	8 (11)	0,48
Treatment complications			
Potassium correction, n (%)	9 (12)	9 (13)	0,88
Phosphate correction, n (%)	9 (12)	31(44)	< 0,01*
Hypoglycemia, n (%)	1 (1)	2 (3)	0,52

Pre-CPG = before implementation of Clinical Practice Guidelines; CPG = after implementation of Clinical Practice Guidelines; DKA = diabetic ketoacidosis; ICU = intensive care unit.

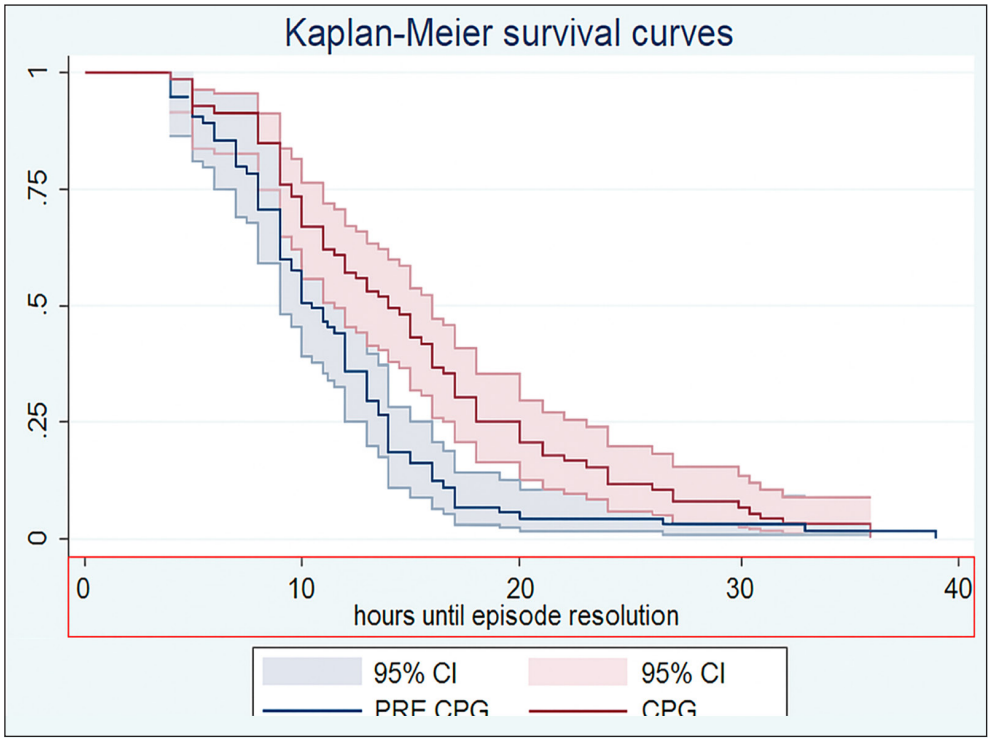

Figure 1. Comparison of time-to-resolution curves of diabetic ketoacidosis episodes before and after the implementation of clinical practice guidelines. Log-rank 0,0008. Pre-CPG = before implementation of Clinical Practice Guidelines; CPG = Clinical Practice Guidelines.

phosphate replacement during treatment- both statistically significant differences.. A difference was also observed in terms of younger age and greater severity in the CPG group, although the latter was not significant.

These differences could be partially explained by the SARS-CoV-2 pandemic, declared by the World Health Organization on March 11, 2020, which led Argentina to implement a "Preventive and Mandatory Social Isolation" policy on March 19, 2020, three months before the institution began implementing the CPGs, which remained in place until December 2022.

Globally, a significant increase in the incidence of T1D has been reported during the pandemic, especially among young children[15-18].

Table 3. Risk factors for cerebral edema in diabetic ketoacidosis

	PRE CPG n = 76	CPG n = 71	p
Patient-related factors			
Age < 5 years, n (%)	8 (11)	14 (20)	0,12
pCO_2 < 21 mmHg, n (%)	18 (24)	20 (28)	0,54
Urea > 40 mg/dL, n (%)	25 (34)	8 (11)	0,01*
New-onset diabetes, n (%)	26 (34)	50 (70)	< 0,01*
Treatment-related factors			
Insulin within the first hour, n (%)	43 (57)	2 (3)	< 0,01*
> 50 mL/kg fluids within first 4 h, n (%)	1 (1,4)	1 (1)	0,98
Sodium decrease > 2 mEq/L per hour, n (%)	33/65 (51)	25/55 (45)	0,62
Bicarbonate correction, n (%)	6 (8)	1 (1)	0,046*

Pre-CPG = before implementation of Clinical Practice Guidelines; CPG = after implementation of Clinical Practice Guidelines.

Table 4. Cox model for the duration of the diabetic ketoacidosis episode

Predictor variables	HR	95% CI		p
CPG	0,62	0,43	0,90	0,017
Age	1,006	1,002	1,009	0,001
pH	48	10	234	0,000
Urea	1,002	0,986	1,02	0,9
Glucose	1	0,99	1,001	0,67
New-onset diabetes	1,49	0,91	2,42	0,1

CPG = clinical practice guidelines; HR = hazard ratio.

Other studies have described a higher frequency of DKA cases, especially severe ones[19,20]. Although SARS-CoV-2 has been proposed to directly damage pancreatic beta cells, the increased disease severity may also be attributed to delayed consultations and diagnosis, leading to more pronounced ketosis, acidosis and total body phosphate depletion

The ICU admission rate observed for the CPG group was higher, although the difference was not statistically significant. Several factors may explain this observation The introduction of standardized criteria for ICU admission through the CPG likely contributed to the apparent increase, representing an improvement in patient safety rather than an adverse outcome. In addition, as reported worldwide, the pandemic period was associated with a rise in DKA severity and, consequently, greater ICU demand[20,21].

Finally, it is also worth noting that the final study period coincided withthe update of the ISPAD Ketoacidosis Treatment Guidelines in 2022[12], in which the the bicarbonate threshold for DKA diagnosis raised from 15 mmol/L to 18 mmol/L. This change increases diagnostic sensitivity, allowing for the identification of mild or moderate DKA cases at earlier stages and, therefore, more timely initiation of treatment, with the potential to prevent complications. In the context of our study, the application of this new classification would have increased the number of cases classified as mild DKA, which could have impacted treatment outcomes, possibly shortening episode duration and reducing phosphate requirements.

This study has several strengths and limitations. Among its strengths, all patients between 1 month and 18 years old diagnosed with DKA and treated in a tertiary PED were included, providing a large and representative sample of a highly complex population. Additionally, the evaluation of CPG adherence allowed a clear assessment of how following standardized recommendation affects clinical outcomes, offering valuable insight into the real-world applicability of the guideline.

One of thelimitations ofthis study are, the retrospective design and absence of a parallel control group wich could limit causal inference, making it difficult to attribute observed changes solely to CPG implementation. . However, the use of advanced statistical models, such as survival analysis and the Cox regression model, allows us to control for possible confounding variables and adjustment for biologically important factors (such as severity and age), which improves the accuracy and reliability of the results.

Further steps were also taken to minimize contamination between study periods- specifically, by excluding 2019 (when the guideline was under development) and 2020 (the year with the most stringent lockdown measures and highest COVID-19 case rates)

Finally, as this study was conducted in a single tertiary care center, the findings may not be generalizable to other institutions. Nevertheless, the proposal CPG includes adaptable recommendations to facilitate its implementation in less complex and resource-limited settings.

Conclusions

The implementation of DKA CPGs in our institution reduced the frequency of treatment-related risk factors for CE, such as the administration of insulin within the first treatment hourand Bic correction. Its implementation was not associated with an increase in complications, although a longer duration of DKA episodes was observed.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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