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Artigo Original

Comparison of the Efficiency of Different Rapid-Acting Insulin Analogues used in Continuous Subcutaneous Insulin Infusion in the Glycaemic Control of Children with Type 1 Diabetes

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A B S T R A C T

Introduction: The use of rapid-acting insulin analogues in continuous subcutaneous insulin infusion as a treatment for type 1 diabetes is considered effective in improving glycaemic control and decreasing the risk of hypoglycaemia. Currently, the available analogues include aspart (Novorapid®), lispro (Humalog®) and glulisine (Apidra®), as well as a new ultra-rapid insulin analogue, faster insulin aspart (Fiasp®). Objective was to compare the impact of different rapid-acting insulin analogues (Novorapid®, Humalog®, Apidra® and Fiasp®) used in continuous subcutaneous insulin infusion in the glycaemic control of children diagnosed with type 1 diabetes.
Methods: Retrospective study including 98 patients diagnosed with type 1 diabetes at age 10 or younger under continuous subcutaneous insulin infusion treatment at Hospital de Braga's Outpatient Paediatric Endocrinology continuous subcutaneous insulin infusion Center.
Results: Regarding the HbA1c values at 3 months, 6 months and 5 years after initiation of continuous subcutaneous insulin infusion, no statistically significant differences were observed between different insulin analogues used (p=0.396, p=0.155 and p=0.518, respectively). The HbA1c values obtained at 12 months and 2 years were significantly higher in Humalog® compared to Fiasp® (p=0.036 and p=0.019, respectively). At 3 years, the HbA1c value of patients with Humalog® was significantly higher than that of patients with Apidra® (p=0.019). The follow-up time for patients with Novorapid® was significantly longer than for those with Apidra® and Fiasp® (respectively, p=0.001 and p=0.023).
Conclusion: Novorapid®, Humalog® and Apidra® have similar efficiency in the glycaemic control of children with type 1 diabetes using continuous subcutaneous insulin infusion. Fiasp® may have benefit in the glycaemic control of these children, when compared with Humalog®. However, it is necessary to conduct further studies, in paediatric age, on the use of this insulin in continuous subcutaneous insulin infusion.

Comparação da Eficácia de Diferentes Análogos de Insulina Rápida Utilizados em Perfusão Subcutânea Contínua de Insulina no Controlo Glicémico das Crianças com Diabetes *Mellitus* Tipo 1

R E S U M O

Introdução: O uso de análogos de insulina de ação rápida em perfusão subcutânea contínua de insulina como tratamento da diabetes *mellitus* tipo 1 é considerado eficaz na melhoria do controlo glicémico e na diminuição do risco de hipoglicemia. Atualmente, os análogos disponíveis incluem aspártico (Novorapid®), lispro (Humalog®), glulisina (Apidra®), e um novo análogo de insulina de ação ultrarrápida, *faster insulin aspart* (Fiasp®).

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Objetivo foi comparar o impacto de diferentes análogos de insulina rápida (Novorapid®, Humalog®, Apidra® e Fiasp®) utilizados em perfusão subcutânea contínua de insulina no controlo glicémico de crianças diagnosticadas com diabetes *mellitus* tipo 1.

Métodos: Estudo retrospetivo com 98 doentes com idade igual ou inferior a 10 anos ao diagnóstico de diabetes *mellitus* tipo 1, sob tratamento com perfusão subcutânea contínua de insulina, seguidos na consulta externa de Endocrinologia Pediátrica no Hospital de Braga.

Resultados: Os valores de HbA1c obtidos aos 3 meses, 6 meses e 5 anos após colocação de perfusão subcutânea contínua de insulina, não foram estatisticamente diferentes entre grupos (p=0,396, p=0,155 e p=0,518, respetivamente). Os valores de HbA1c aos 12 meses e 2 anos foram significativamente superiores na Humalog® em relação à Fiasp® (p=0,036 e p=0,019, respetivamente). O valor de HbA1c aos 3 anos foi significativamente superior na Humalog® em relação à Apidra® (p=0,019). O tempo de *follow-up* dos doentes com Novorapid® foi significativamente superior ao dos com Apidra® e Fiasp® (respetivamente, p=0,001 e p=0,023).

Conclusão: As insulinas Novorapid®, Humalog® e Apidra® têm uma eficácia semelhante no controlo glicémico das crianças com diabetes *mellitus* tipo 1 com perfusão subcutânea contínua de insulina. A insulina Fiasp® poderá ter benefício no controlo glicémico destas crianças, comparativamente à Humalog®. No entanto, é necessário realizar mais estudos, em idade pediátrica, acerca do uso desta insulina em perfusão subcutânea contínua de insulina.

Introduction

Type 1 diabetes (T1DM) is a disease characterized by chronic hyperglycaemia caused by autoimmune destruction of pancreatic β cells and consequent insulin deficiency, and is considered the most common chronic disease in school-aged children.[1]

The first-line treatment for T1DM is insulin therapy, which should be initiated at the time of diagnosis, and consists of insulin administration to mimic its physiological secretion, including basal insulin (long-acting) and prandial insulin (short-acting). Insulin therapy aims to achieve good glycaemic control (the general goal is to achieve an HbA1c value of less than 7%) and to prevent macro and microvascular complications of the disease, maintaining the quality of patients lives and ensuring adequate height and weight development.[2,3]

Continuous subcutaneous insulin infusion (CSII) as a form of intensive treatment is currently considered the best way to mimic the physiological profile of insulin release. Using short acting insulin allows programming a basal infusion rhythm and a bolus release according to carbohydrate intake and the pre-meal glucose value.[3] CSII is effective in improving glycaemic control and in decreasing the risk of severe hypoglycaemia, with the advantage of allowing greater flexibility and freedom in lifestyle, particularly beneficial in cases of children with varying and unpredictable eating patterns.[3–6] The most frequent complications associated with the use of CSII are infection of the infusion site or obstruction of the catheter and, consequently, glycaemic decompensation with hyperglycaemia with ketosis, or even ketoacidosis.

The American Diabetes Association and the International Society for Paediatric and Adolescent Diabetes (ISPAD) treatment recommendations include several short-acting insulin formulae approved for use in paediatric age, namely fast-acting insulin analogues. They are widely recommended for use in CSII and have a 10 to 15 minutes onset, one to three hours peak of action and three to five hours duration. Currently available fast-acting insulin analogues include aspart (Novorapid®), lispro (Humalog®) and glulisine (Apidra®).[3,7] Humalog® was the first fast-acting insulin analogue to be developed and is available for use in adult and paediatric patients since 1996.[8] Novorapid® was made available in 1999 and Apidra® became globally available in 2004, and is indicated as treatment in children aged 6 years and over, while the other fast-acting insulin analogues can be started in children under the age of 6.[8–10] Despite having different chemical properties, the pharmacodynamic profiles of these three insulins do not result in clinically significant differences. Administration is recommended between zero up to 15 minutes before a meal, however, in specific cases as in young children with unpredictable eating patterns, administration immediately after a meal is possible.[8]

There is also a new ultra-fast-acting insulin analogue, faster insulin aspart (Fiasp®), produced by adding the niacinamide and L-arginine excipients to the Novorapid® insulin, resulting in an increased insulin absorption rate. The peak and duration of action are similar to that of Novorapid®, but the onset of action is even shorter (5 to 10 minutes). Fiasp® was approved by the European Commission in 2017 for use in adults, adolescents and children aged one year or over, after the pharmacokinetic and pharmacodynamic profiles seen in adults were also observed in children and adolescents.[3,11,12]

Through a retrospective analysis of observational longitudinal data, the present study will compare the insulin analogues mentioned above regarding their efficacy in CSII in children with T1DM. Our aim is to assess whether any one of these provides better glycaemic control compared to the others, through the analysis of HbA1c values at 3, 6 and 12 months, and 2, 3 and 5 years after initiation of CSII.

Methods

Study design and patient selection

This was an observational, analytical and retrospective study regarding all children aged 10 years or younger at T1DM diagnosis, followed or referred for CSII treatment from other hospitals to Hospital de Braga's Outpatient Paediatric Endocrinology Consultation between January 2009 and January 2020, using a CSII system.

To sample selection the following inclusion criteria were used: T1DM diagnosis, age of diagnosis ≤10 years and use of CSII. Patients were excluded if they changed their fast-acting insulin analogue, due to lack of records of the insulin analogue used or registry of HbA1c values.

One hundred and six patients under treatment at the Hospital de Braga's Outpatient Paediatric Endocrinology Consultation diagnosed with T1DM and aged 10 years or less at diagnosis were identified. Nine patients were excluded from the study because they did not use a CSII system, seven because they had changed their insulin analogue during the use of CSII, one because the insulin analogue used was not recorded, and one because the HbA1c value was not recorded during the time of the study. A final sample of 98 patients was obtained.

An additional analysis of the patients who changed their insulin analogue used was included, to compare the glycaemic control of older insulin analogues with the recent Fiasp®. That sample included six patients.

Study variables and data gathering

The patients clinical records were consulted, and clinical information regarding sociodemographic data (birth date and sex), priors regarding their T1DM (age, serum glucose value and HbA1c value at diagnosis, date of CSII initiation, HbA1c value, insulin dosage and fast-acting insulin analogue used at CSII initiation) and follow-up (follow-up time, HbA1c value and daily insulin dose per weight at 3, 6, 12 months, 2, 5 and 10 years after CSII initiation) data were recorded.

Statistical analysis

Statistical analysis was performed using the International Business Machine® (IBM) Statistical Package for the Social Sciences® (SPSS) software, version 26. A significance level of 5% was established, with $p < 0.05$ deemed as statistically significant.

The sample was categorized into four groups according to the insulin analogue used. In each group, in order to assess the distribution of continuous variables, the significance of the Kolmogorov-Smirnov and Shapiro-Wilk tests was verified, and the Q-Q plot, the histogram and the asymmetry and kurtosis values were also analysed.[13,14]

The quantitative variables under study did not have a normal distribution. As such, nonparametric tests were performed. For this same reason, the median (Mdn) was the measure of central tendency analysed and the interquartile range (IQR) was considered as a measure of dispersion. Continuous variables were analysed according to the result of the Kruskal-Wallis test, with calculation of the eta squared (η2).[15]

Categorical variables were expressed as absolute (n) and percentage (%) values and compared using Pearson Chi-square test (χ^2). The effect size was determined using Cramer V coefficient (V), which was considered weak, medium, or strong, respectively for values of 0.06; 0.17 and 0.29; giving 3 degrees of freedom.[16]

The Kruskal-Wallis test was used to perform multiple comparisons on continuous variables, with significance values adjusted by the Bonferroni correction.

To compare the glycaemic control of patients before and after switching from older insulin analogues to Fiasp®, a paired samples t test (*t*) was used.

Ethical considerations

This study was approved by the Ethics Committee for Research in Life and Health Sciences of the University of Minho and by the Hospital de Braga Ethics Committee.

The patients anonymity and confidentiality were safeguarded with an identification code assigned to the file number of each patient. The information collected does not allow the identification of patients.

Results

Descriptive characterization of the study population is described in Table 1.

Patients selected were divided into 4 groups and compared according to the insulin used. Thus, group 1 corresponds to patients using Novorapid®, group 2 corresponds to Humalog®, group 3 corresponds to Apidra® and group 4 corresponds to Fiasp®. The comparison of the quantitative variables under study for each of these groups is summarized in Table 2.

Table 1. Type 2 Diabetes remitters and non-remitters' characteristics

	n (%)
Sex (female)	52 (53.1%)
Novorapid®	50 (51.0%)
Humalog®	12 (12.2%)
Apidra®	25 (25.5%)
Fiasp®	11 (11.2%)
	Mdn (IQR)
Follow-up time (years) n=98	68 (45)
Glucose at T1DM diagnosis (mg/dL) n=95	479 (205)
HbA1c at T1DM diagnosis (%) n=89	11.0 (2.8)
HbA1c at CSII initiation (%) n=94	8.1 (1.4)
HbA1c 3 months after CSII initiation (%) n=89	7.7 (1.2)
HbA1c 6 months after CSII initiation (%) n=88	7.5 (1.3)
HbA1c 12 months after CSII initiation (%) n=76	7.6 (1.1)
HbA1c 2 years after CSII initiation (%) n=65	7.8 (1.0)
HbA1c 3 years after CSII initiation (%) n=43	7.5 (1.3)
HbA1c 5 years after CSII initiation (%) n=22	8.0 (1.1)
Insulin dosage at CSII initiation (U/kg/day) n=84	0.70 (0.37)
Insulin 3 months after CSII initiation (U/kg/day) n=83	0.71 (0.30)
Insulin 6 months after CSII initiation (U/kg/day) n=87	0.75 (0.23)
Insulin 12 months after CSII initiation (U/kg/day) n=77	0.80 (0.22)
Insulin 2 years after CSII initiation (U/kg/day) n=60	0.84 (0.21)
Insulin 3 years after CSII initiation (U/kg/day) n=43	0.86 (0.22)
Insulin 5 years after CSII initiation (U/kg/day) n=22	0.81 (0.19)
Follow-up time (years) n=98	4.8 (5.0)

Mdn - median; IQR - interquartile range; HbA1c - glycated haemoglobin; CSII - continuous subcutaneous insulin infusion; T1DM - type 1 diabetes mellitus

Regarding the sex of the patients, there were no statistically significant differences between the groups ($\chi^2(3)=0.084$; p=1.000; V=0.029), with females comprising 54% of patients using Novorapid® (n=27), 50% using Humalog® (n=6), 52% using Apidra® (n=13) and 54.5% using Fiasp® (n=6). Regarding age at T1DM diagnosis ($p=0.325$), blood glucose at diagnosis ($p=0.218$), HbA1c value at diagnosis ($p=0.106$) and HbA1c value at the date of CSII initiation ($p=0.897$), no statistically significant differences were observed between the four groups. There were also no statistically significant differences between the HbA1c values obtained 3 months ($p=0.396$) and 6 months ($p=0.155$) after CSII initiation. Regarding the value of HbA1c 5 years after CSII initiation, there were also no significant differences between groups ($p=0.518$), however it was not possible to obtain Mdn or IQR in groups 2, 3 and 4 as in group 2 and 3 there was only one case registered (n=1) and group 4 does not have a 5 year follow-up time yet. Regarding the daily insulin dose, there were no statistically significant differences in any of the moments under study, namely at CSII initiation date ($p=0.050$), after 3 months ($p=0.095$), 6 months ($p=0.066$), 12 months ($p=0.955$), 2 years ($p=0.267$), 3 years ($p=0.059$), and 5 years ($p=0.341$).

The HbA1c values obtained 12 months (p=0.036; $\eta^2=0.05$) and 2 years (p=0.019; $\eta^2=0.08$) after CSII initiation were significantly higher in patients using Humalog® than those who used Fiasp®, with no statistically significant differences between the other groups. At 3 years, the HbA1c value of patients using Hum-

Table 2. Comparison of the variables under study by type of insulin analogue used.

	Group 1 Novorapid® (n=50) Mdn (IQR)	**Group 2 Humalog® (n=12)** Mdn (IQR)	**Group 3 Apidra® (n=25)** Mdn (IQR)	**Group 4† Fiasp® (n=11)** Mdn (IQR)	***p***	**H**	**η^2**
Age at diagnosis (months) n=98	66,. (45)	86 (44)	83 (45)	71 (75)	0.325	3.469	0.02
Glucose at diagnosis (mg/dL) n=95	472 (221)	504 (114)	560 (254)	538 (254)	0.218	4.435	0.01
HbA1c at diagnosis (%) n=89	10.4 (2.7)	12.1 (2.2)	11.3 (2.4)	10.1 (2.2)	0.106	6.124	0.01
HbA1c initiation (%) n=94	8.1 (1.1)	8.2 (0.9)	7.85 (2.0)	8.35 (2.7)	0.897	0.599	0.05
HbA1c 3 months (%) n=89	7.6 (0.8)	8.1 (1.9)	7.6 (1.3)	8.1 (2.7)	0.396	2.971	0.02
HbA1c 6 months (%) n=88	7.5 (0.9)	7.9 (1.5)	8.0 (1.5)	6.9 (0.7)	0.155	5.242	0.00
HbA1c 12 months (%) n=76	7.45 (1.0)	8.35 (1.7)	7.85 (1.5)	7.05 (1.2)	0.036*	8.567	0.05
HbA1c 2 years (%) n=65	7.8 (0.8)	8.65 (1.8)	7.9 (1.6)	6.9 (1.5)	0.019*	9.988	0.08
HbA1c 3 years (%) n=43	75 (1.3)	9.8 (-)	7.2 (1.2)	7.15 (-)	0.019*	9.942	0.13
HbA1c 5 years (%) n=22	7.9 (1.1)	-	-	-	0.518	2.273	0.15
Insulin initiation (U/kg/day) n=84	0.77 (0.30)	0.90 (0.70)	0.58 (0.38)	0.62 (0.28)	0.050	7.814	0.04
Insulin 3 months (U/kg/day) n=83	0.78 (0.29)	0.86 (0.34)	0.64 (0.44)	0.67 (0.22)	0.095	6.365	0.02
Insulin 6 months (U/kg/day) n=87	0.77 (0.21)	0.84 (0.35)	0.70 (0.31)	0.70 (0.28)	0.066	7.185	0.03
Insulin 12 months (U/kg/day) n=77	0.80 (0.21)	0.80 (0.39)	0.80 (0.37)	0.82 (0.18)	0.955	0.326	0.06
Insulin 2 years (U/kg/day) n=60	0.83 (0.17)	0.90 (-)	0.84 (0.31)	0.70 (0.33)	0.267	3.953	0.02
Insulin 3 years (U/kg/day) n=43	0.84 (0.20)	0.90 (-)	0.95 (0.45)	0.69 (-)	0.059	7.456	0.06
Insulin 5 years (U/kg/day) n=22	0.80 (0.18)	-	-	-	0.341	3.350	0.09
Follow-up tim e (years) n=98	6.7 (3.7)	3.75 (6.4)	2.7 (4.4)	1.33 (6.6)	0.001*	22.977	0.19

† The number of patients in FIasp® follow-up time points was: 2 patients at 3 years follow-up, 4 patients at 2 years follow-up and 6 patients at 12 months follow-up.

* $p<0.05$; H – Kruskal-Wallis test value; η^2 - eta squared; Mdn - median; IQR - interquartile range; HbA1c - glycated haemoglobin.

alog® was significantly higher than that of patients using Apidra® ($p=0.019$; $\eta^2=0.13$), with no statistically significant differences between the remaining groups. The follow-up time for patients using Novorapid® was significantly longer than those using Apidra® and Fiasp® ($p=0.001$; $\eta^2=0.19$). The detailed results of the multiple comparisons between groups, for the variables analysed, are described in Table 3.

Table 3. Multiple comparisons between groups for variables where statistically significant differences were observed.

	HbA1c 12 months *Adjusted Sig.* †	**HbA1c 2 years** *Adjusted Sig.* †	**HbA1c 3 years** *Adjusted Sig.* †	**Follow-up (years)** *Adjusted Sig.* †
Apidra – Fiasp	0.314	0.256	1.000	1.000
Apidra – Humalog	0.778	0.476	0.016*	1.000
Fiasp – Humalog	0.032*	0.012*	0.116	1.000
Apidra – Novorapid	1.000	1.000	0.782	0.001*
Fiasp – Novorapid	0.748	0.363	1.000	0.023*
Humalog – Novorapid	0.184	0.131	0.103	0.062

† Significance values adjusted using Bonferroni correction for multiple comparison.

* $p<0.05$; HbA1c - glycated haemoglobin

Table 4. Comparative analysis of variations in glycated haemoglobin in patients that transitioned from an older insulin analogue to Fiasp®.

	HbA1c	***p***	***t***	***d***	***n***
Before Fiasp® *vs* 3 months after Fiasp®	7.97 *vs* 7.7	0.650	0.529	0.244	3
Before Fiasp® *vs* 6 months after Fiasp®	7.93 *vs* 7.78	0.691	0.438	0.190	4
Before Fiasp® *vs* 12 months after Fiasp®	8.08 *vs* 7.76	0.407	0.926	0.374	5

t – paired samples t test result; *d* – Cohen's d; *n* – number of cases

Discussion

In the present study, the results obtained regarding the efficacy of the rapid-acting insulin analogues Novorapid®, Humalog®, Apidra® and Fiasp® in the glycaemic control of children with T1DM and CSII were similar. However, there was a trend towards worse glycaemic control with Humalog® insulin, with some HbA1c values statistically higher than with the other insulins. Fiasp® has been shown to have a possible positive association in the glycaemic control of these children, with HbA1c values tending to be lower (and some statistically lower), with lower doses of insulin, although no statistically significant differences were observed for this variable.

When compared to Fiasp®, Humalog® obtained significantly higher HbA1c values both at 12 months and at 2 years after CSII initiation. No statistically significant difference was observed at 3 years. This result can be explained by the small number of cases registered in both groups in the period in question. It was not possible to make a comparison at 5 years, since Fiasp® has only been in use since 2017.[11] The Humalog® insulin group obtained statistically higher HbA1c values at 3 years than the Apidra® insulin group. This result differs from the one obtained in a 2009 review, which compares Apidra® with the other fast acting insulin analogues, where no statistically significant differences were observed between these two insulins in glycaemic control.[17] However, this result may be explained by the fact that there are few cases to compare.

When comparing Novorapid® and Humalog®, no statistically significant differences were found in any of the studied variables. This is in line with an open-label, prospective study, comparing 2 groups of children and adolescents aged 4 to 18 years, assigned to receive either Novorapid® or Humalog®, in which no statistically significant differences were observed, particularly in the HbA1c values, among children who used these insulins.[18] The absence of statistically significant differences in the follow-up time of these patients is supported by the fact that both Humalog® and Novorapid® were introduced to the market at approximately the same time, in 1996 and 1999 respectively, and both can be started in children at preschool age (<6 years).[8,9]

There were no statistically significant differences between the glycaemic control of children using Novorapid® and Fiasp®. This result is consistent with what is described in the literature, as we can find in a review published in 2019, were non-inferiority of Fiasp® over Novorapid® in terms of change from baseline in HbA1c was confirmed but superiority of Fiasp® over Novorapid® in terms of HbA1c reduction was not confirmed.[19] Nevertheless, a randomized, multicentre, treat-to-target, phase 3 trial, published in 2018, showed that the estimated odds of achieving HbA1c targets with Fiasp® were not significantly different from those with Novorapid®, but the estimated treatment difference of changes from baseline in HbA1c levels significantly favoured Fiasp®.[20] Another randomized, double-blind, parallel-group, actively controlled trial, showed similar results, with a better glycaemic control observed with Fiasp® when compared Novorapid®, however, these observations were not statistically significant.[21] Statistically significant differences were found regarding the follow-up time of these children, which in Novorapid® was significantly higher. This can be explained by the fact that Novorapid® has been available for use in paediatric age since 1996, while Fiasp® insulin is a recent formulation, available only since 2017.[9,11]

Apidra® and Novorapid® showed no statistically significant differences in the glycaemic control of patients. As in our study, a prospective, open-label, randomized controlled trial, designed to show the superiority of Apidra® over Humalog® and Novorapid® failed its main objective, reporting that there were no statistically significant differences between them.[22] Kamal and Bain, upon reviewing the literature, also expressed the opinion of the similar glycaemic control of Apidra® when compared with other insulins, namely Novorapid®.[23] However, the follow-up time of children using Novorapid® was significantly longer, which may be explained by the fact that this insulin can be started from 2 years of age, in contrast to Apidra®, which is indicated in children over the age of to 6.[8,10] Thus, in children with an earlier diagnosis (<6 years), Novorapid® will be introduced preferentially, and consequently these children will have a longer follow-up time.

Among the groups of children using Apidra® and Fiasp®, no statistically significant differences were observed in any variable under study. There are not yet enough studies comparing these two insulins. This result would be expected since fast-acting insulin analogues have similar pharmacological profiles.

Regarding the total daily insulin dose, although no statistically significant differences were observed between the groups, it is noticeable that these values tend to increase over time after the CSII initiation, contrary to what is described in similar studies, which observed a decrease in these values after CSII initiation,[5] but in this study we did not compare the dose of insulin after CSII initiation with the previous dose used in multiple daily administrations. CSII is described to allow lower doses of insulin to be used, when compared to the multiple daily administrations regimen.[3] However, there is still no consensus on the impact of the different insulins used in relation to this variable, with some studies describing no differences between insulins, while others report the need for lower insulin doses with Novorapid® and Apidra®, when compared with Humalog®.[18,22,23]

The rapid-acting insulin analogues Novorapid®, Humalog® and Apidra® have similar effectiveness in the glycaemic control of children with T1DM. However, this study demonstrated a possible positive association in terms of glycaemic control with the use of Fiasp®. These results are in agreement with ISPAD guidelines, which state that ultra-fast-acting insulins aim to mimic the action profile of prandial insulins even more effectively and are able to respond more quickly to the increase in blood glucose after meals. This might make them particularly useful in patients with CSII.[3]

To better characterize the findings of a possible positive association with Fiasp® and glycaemic control, an analysis of glycaemic control of patients that transitioned from older insulin analogues to the newer one, Fiasp®, was included in this study. Those results did not reveal any statistically significant changes in the glycaemic control at any time point after the insulin analogue change. To this point, the literature is supportive of these findings regarding the similar efficacy of the insulin analogues on glycaemic control.[20] However, we did not find any study comparing the glycaemic control of the same patients before and after Fiasp® initiation.

For a better interpretation of this study, it is important to consider its limitations. First, as this is a non-randomized, observational study, all results can only be interpreted as associations and never as causality. Second, as this is a retrospective study, the sample size was conditioned by the number of patients previously followed up on Hospital de Braga. Third, considering that the selected cases were categorized into four different groups, with different sample sizes, the conclusions to be drawn from the statistical analysis have limitations. It was also not possible to ensure a lower number of cases omitted in the statistical analysis of some variables, due to the lack of registry of HbA1c values in certain patients. It is essential that, in the future, HbA1c values of patients with T1DM are recorded methodically throughout the follow-up period, in order to allow for a more accu-

rate assessment of glycaemic control. Another important limitation of this study is the short time of clinical use of Fiasp®, which results in a short follow-up time and a small sample of patients in this group. Finally, it is possible that the statistical differences observed are due to better glycaemic control not only provided for the insulin itself but due to an overall improvement in medical care, for instance, the introduction of continuous or intermittent glucose monitoring; as this data were not available, this is another limitation of the present study.

Conclusion

This study allowed us to conclude that the efficacy of the fast-acting insulin analogues Novorapid®, Humalog® and Apidra® in the glycaemic control of children with T1DM with CSII is similar. In this study, the ultra-fast-acting insulin Fiasp® revealed an association with better glycaemic control. However, more studies, namely prospective, randomized and with a larger sample size are needed to prove the benefits of using this ultra-fast-acting insulin in paediatric age, to the detriment of the other fast-acting insulins available.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.
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Ethical Disclosures

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).
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