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Original Research

Efficacy of low-dose insulin combined with electrolyte in the treatment of pediatric diabetic ketoacidosis and its effect on serum inflammatory factors

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Abstract: Diabetic ketoacidosis (DKA) is a very serious disease that can occur in both types of diabetes (type 1 and 2). It is caused by a combination of high blood sugar and low insulin levels, which can cause the body to produce too much ketone. Ketones are toxic to human organs. This research aimed to investigate the clinical efficacy of low-dose insulin combined with electrolyte in the treatment of pediatric DKA and its effect on serum inflammatory factors. For this purpose, a total of 122 children with DKA admitted to our hospital from April 2013 to May 2016 were selected as research objects. They were divided into group A with 60 cases and group B with 62 cases. Group B was treated with supplemental electrolytes, and group A was treated with low-dose insulin based on group B. The serum levels of TNF-α, IL-6, and IL-18 were measured by enzyme-linked immunosorbent assay (ELISA) before and after treatment, and the blood sugar, sodium, and potassium levels were measured by an automatic biochemical analyzer. The time when blood sugar reached the standard level when acidosis was corrected and hospitalization time was compared between the two groups. The total effective rate of group A was significantly higher than that of group B ($p< 0.05$). There was no significant difference in blood glucose, sodium, potassium, TNF-α, IL-6, and IL-18 levels between the two groups before treatment. (all $p > 0.05$). But the blood glucose, sodium and potassium levels in group A were significantly better than those in group B (all $p< 0.001$). The levels of serum TNF-α, IL-6, and IL-18 in group A were significantly lower than those in group B after treatment (all $p< 0.001$). After treatment, the time when blood sugar reached the standard level when acidosis was corrected and hospitalization time in group A were significantly shorter than those in group B (all $p< 0.001$). Low-dose insulin combined with electrolyte supplementation is effective in the treatment of DKA in children, which can effectively control blood sugar, sodium, potassium level, and inflammatory factor concentration.

Key words: Diabetic ketoacidosis in children; Low-dose insulin; Electrolyte supplementation; Clinical efficacy; Inflammatory factor.

Introduction

Diabetic ketoacidosis (DKA) is an acute complication of diabetes. This complication is characterized by three biochemical characteristics: ketosis, acidosis and hyperglycemia. The DKA may be an early sign of type 1 diabetes, but it is usually when the level of insulin in the blood is lower than the body's needs (for example, forgetting the insulin dose or increasing the insulin dose under stressful conditions such as illness Bottom) diagnosed with diabetes and surgery. The DKA is characterized by shortness of breath, shortness of breath with ketone smell, nausea and vomiting, dehydration and abdominal pain or decreased consciousness. Treatment is a specialized treatment that usually requires emergency care in the intensive care unit. The main methods of treatment are hydration and control of sugar and acidosis (1-5). The DKA is a common disease in pediatrics and is a serious complication caused by diabetes in children. It is mainly caused by severe insufficiency of insulin and abnormal increase of blood sugar hormone, leading to metabolic disorders of related substances (1,2). The main symptoms of the disease are nausea, vomiting, polyuria, dehydration, and abdominal pain, which is characterized by rapid progress and sudden illness (3). If not timely treated, the children will be comatose or even dead (4). Therefore, exploring the appropriate treatment of DKA has always been a hot spot in clinical research (5, 6).

In clinical practice, due to electrolyte disturbance and dehydration in children, timely supplementation of electrolytes not only greatly improves renal function and blood circulation function, but also accelerates the discharge of acidosis substances into the body with urine, and at the same time, better reduce blood sugar levels (7). Previous treatment of DKA in the clinic often adopted the methods of active and effective fluid replacement and insulin injection. Because the blood osmotic pressure drops suddenly after high dose injection, complications such as hypoglycemia and brain edema often occur. Therefore, in recent years, the use of low-dose insulin injection gradually replaces high dose insulin injection, and the effect is satisfactory (8, 9). Recent studies have shown that increased levels of inflammatory factors such as TNF-α, IL-6, and IL-18 have also been detected in DKA patients (10-12). Although the mecha-

nism is not yet clear, it suggests that inflammation is closely related to the occurrence and development of diabetes mellitus, even inflammatory cytokines may play an important role in the development of DKA.

Clinical treatment of DKA children mainly aims to correct electrolyte disorder, acid-base imbalance, and hypoglycemia (13). However, there is little treatment for DKA children with low-dose insulin combined with electrolyte. In this study, low-dose insulin was given while electrolyte supplementation was used in DKA children. The changes of inflammatory factors TNF-α, IL-18, and IL-6 were observed in the treatment, so as to provide a reference for the treatment of children with DKA.

Materials and Methods

General information

A total of 122 children with DKA admitted to our hospital from April 2013 to May 2016 were selected as study subjects. They were divided into group A (60 patients) and group B (62 patients). The two groups were treated with supplemental electrolytes. Based on this, group A was treated with low-dose insulin. Group B was treated with large dose insulin, and 0.1-0.20 U/(kg·h) of insulin was given to patients with a subcutaneous injection before bedtime, once a day. There were 32 males and 28 females in group A, aged 1 to 11 years, with an average age of 6.19 ± 1.86 years; 36 males and 26 females in group B, aged from 2 to 11 years, with an average age of 6.37 ± 1.52 years. Inclusion criteria: All children were diagnosed in accordance with the diagnostic criteria for the Guidelines for Diagnosis and Treatment of DKA in Children; their age was less than 12 years old; this study was not against ethics and morality, and the program was submitted to the Hospital Ethics Committee for review and approval; the guardians of children voluntarily signed the informed consent document. Exclusion criteria: patients with cerebral edema, and septic shock; 6 hours without urine; accepted insulin therapy before admission; patients with severe liver and kidney dysfunction, malignant tumor; patients with congenital heart disease, congenital neuropathy, dilated cardiomyopathy, heart failure, cardiogenic shock and malignant tumors.

Treatment methods

Two groups of children were treated with symptomatic treatment and supportive treatment after admission. Group B was treated with electrolyte supplementation. After admission, the children were given routine tests and oxygen inhalation, and electrolyte, blood sugar, and blood gas experiments in time. The severity of acidosis and dehydration was evaluated scientifically, and symptomatic treatment was given in time. For children with moderate or severe DKA, intravenous channels should be established in time and physiological saline should be completely given within 60min with a dose of 10-20 ml/kg. When the peripheral circulation is poor, repeated treatment is required. Sodium chloride with 0.45% concentration at the initial speed of 10 mL (kg. H) was given immediately. After 60-120 minutes of installation, the speed was adjusted to 5 mL(kg·h), and the drip rate was adjusted based on the physical condition. When there is no contraindication of potassium solution in children, potassium solution should be added to normal saline and sodium chloride. On this basis, the second channel was established to drip insulin (Jiangsu Wanbang Biochemical and Pharmaceutical Co., Ltd., batch number: H32024567). In group A, insulin was given 0.1 U (kg/·h); in group B, insulin was given 0.2 U (kg·h). If the blood sugar level was still above 15 mmol/L, the insulin input would be increased by 25%. If the blood sugar level was below 8 mmol/L, the sugar input concentration would be increased by 10% on the original basis, and the insulin infusion dose would be kept at 0.05 U/kg per hour.

Main instruments and reagents

TNF-α enzyme-linked immunosorbent assay (ELISA) kit was purchased from Shanghai Xiyuan Biological Technology Co., Ltd., China, batch number: XY-BGK01375. IL-18 and IL-6 ELISA diagnostic kits were purchased from Shanghai Guduo Biology Co., Ltd., China, with the numbers GD-G10207 and GD-G10211, respectively. A fully automatic biochemical analyzer is manufactured in Human, Germany, batch number: 16660. ELISA is manufactured in Molecular Devices, USA, batch number: SpectraMaxiD5.

Observation indicators

The corrective time of acidosis, the time of blood sugar reaching the standard, and the time of hospitalization were observed and recorded in the two groups. Blood glucose, serum potassium, serum potassium levels, serum inflammatory factors (IL-6, IL-18, TNF-α) were measured before and after treatment. Blood glucose, serum potassium, and potassium levels were detected by an automatic biochemical analyzer. Serum TNF-α, IL-6, and IL-18 concentrations were detected by ELISA: standard wells, sample wells, and blank control wells were set up (not add sample and enzyme-labeled reagent), the enzyme label is accurately loaded with 50μl of the standard on the plate, and add 40μl of the sample diluent, then 10μl of the sample to be tested in the sample wells (the final dilution of the sample is 5 times). Then the wells were covered with the membrane, incubate at 37℃ for 30 min; discard the liquid in each well, pat dry, repeat washing 5 times; add 50μl of enzyme labeling reagent to each well except for blank wells, cover with a membrane, incubate at 37 ℃ for 30 min; add 50μl chromogenic reagent A to each well, then add 50μl developer B, mix and develop color at 37 ℃ for 10 min in the dark; add 50μl stop solution to each well to terminate the reaction. The absorbance (OD) of each hole was measured sequentially at 450nm wavelength by ELISA detector, and the concentration of IL-6, IL-18, and TNF-α was calculated.

Efficacy judgment are 1) markedly effective: the symptoms of the child basically disappeared, the ketone body turned negative, and the blood sugar returned to normal, 2) effective: the symptoms of the child improved significantly, the ketone body (+), and the blood sugar was slightly higher than the normal value, and 3) invalid: No significant change or even aggravation of symptoms and indicators in children. Significant efficiency + effective rate = the total efficiency.

Table 1. General information of group A and group B (n(%))/(x±sd).

Factors	Group A (n=60)	Group B (n=62)	T/χ^2 value	P-value
Gender			0.277	0.599
Male	32(53.33)	36(58.06)		
Female	28(46.67)	26(41.94)		
Age	6.19±1.86	6.37±1.52	0.586	0.559
Weight (kg)	20.05±2.34	19.56±2.25	1.179	0.241
Height (cm)	116.13±5.25	115.65±5.91	0.474	0.637
BMI	12.62±2.85	12.24±3.12	0.702	0.484
Place of residence			0.288	0.591
City	47(78.33)	46(74.19)		
Rural	13(21.67)	16(25.81)		
Parental alcoholism history			0.458	0.498
Yes	16(26.67)	20(32.26)		
No	44(73.33)	42(67.74)		
Parental smoking history			0.109	0.742
Yes	24(40.00)	23(37.10)		
No	36(60.00)	39(62.90)		
Nationality			0.118	0.731
Minority	8(13.33)	7(11.29)		
Han nationality	52(86.67)	55(88.71)		
Mother's education			0.581	0.446
Below high school	12(20.00)	16(25.81)		
High school and above	48(80.00)	46(74.19)		
pH value	7.29±0.13	7.28±0.16	0.378	0.706
HbA1c	13.24±2.27	12.98±2.35	0.621	0.536

Table 2. Comparison of clinical efficacy results between group A and group B (n(%)).

Category (cases (%))	Group A (n=60)	Group B (n=62)	χ^2 value	P value
Significant effect	32(53.33)	26(41.94)	-	-
Effective	23(38.33)	20(32.26)	-	-
Invalid	5(8.33)	16(25.81)	-	-
Total treatment efficiency	55(91.67)	46(74.19)	6.533	0.011

Statistical methods

Statistical analysis was performed using SPSS 21.0 (IBM Corp, Armonk, NY, USA). Counting data were expressed by case/percentage (n (%)). A Chi-square test was used to compare the counting data between groups. Mean ± standard deviation (x±sd) was used to express the measurement data. An independent sample t-test was used to compare the measurement data between groups, but the paired t-test was used to compare before and after the same group. When $p< 0.05$, the difference was statistically significant.

Results

Two groups of general information

There was no significant difference in gender, age, weight, height, weight, residence, parental alcoholism history, parental smoking history, ethnicity and maternal education level between group A and group B (all $p> 0.05$, Figure 1).

Comparison of clinical efficacy between group A and group B

After treatment, 32 cases (53.34%) were markedly effective, 23 cases (38.33%) were effective, 5 cases (8.33%) were ineffective, and the total effective rate was 91.67% in group A. After treatment, 26 cases (41.93%) were markedly effective, 20 cases (32.26%) were effective, 16 cases (25.81%) were ineffective, and the total effective rate was 74.19% in group B. Obviously, the total effective rate in group A after treatment was significantly higher than that in group B ($p< 0.05$, Table 2).

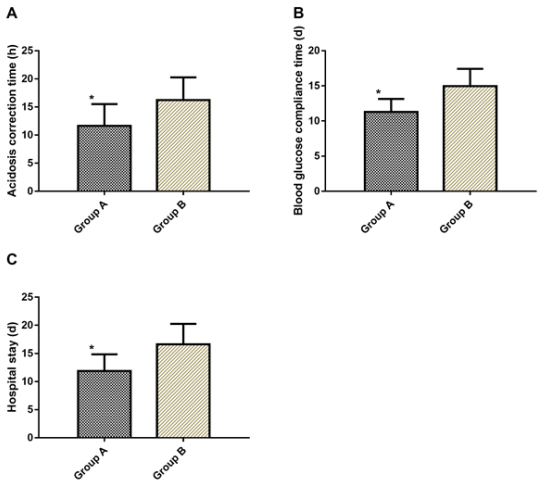

Figure 1. Comparison of treatment effects between group A and group B, * indicated $p< 0.05$, compared with group B.

Table 3. Comparison of treatment effects between group A and group B ($\overline{x} \pm sd$).

Group	cases	Acidosis correction time (h)	Blood glucose compliance time (d)	Hospitalization (d)
Group A	60	11.64±3.86	11.29±1.86	11.89±2.95
Group B	62	16.22±4.05	14.95±2.48	16.64±3.61
T value	-	6.341	9.145	7.892
P value	-	< 0.001	< 0.001	< 0.001

Comparisons of acidosis correction time, blood glucose achievement time and hospitalization time between group A and group B

The time when acidosis was corrected, the time when blood sugar reached the standard level and the time of hospitalization in group A were significantly shorter than those in group B. There was a significant difference between the two groups based on Table 3 & Figure 1(all $p< 0.05$).

The time when acidosis was corrected in group A and group B was compared (A), and the correction time of acidosis in group A was significantly shorter than that in group B ($p< 0.05$). The time when blood sugar reached the standard of group A and group B was compared (B), and the time when blood sugar reached the standard of group A was significantly shorter than that of group B. The hospitalization time of group A and group B were compared (C), and the hospitalization time of group A was significantly shorter than that of group B.

Changes in blood glucose, serum potassium and blood sodium concentration before and after treatment in group A and group B

There were no significant differences in serum glucose, serum potassium, and serum sodium levels between group A and group B before treatment (all P> 0.05). The blood glucose and serum sodium levels in group A and group B were significantly lower than the pre-treatment levels (both $p< 0.05$), while the serum potassium levels were significantly higher than the pre-treatment levels ($p< 0.05$). After treatment, the blood glucose and serum sodium levels in group A were significantly lower than those in group B (both $p< 0.05$), while the serum potassium level was significantly higher than that in group B based on Table 4 & Figure 2 ($p< 0.05$).

Comparison of blood glucose levels before and after treatment in group A and group B (A), there was no significant difference in serum glucose levels between group A and group B before treatment (both P> 0.05). The blood glucose levels in group A and group B were significantly lower than those before treatment (both $p< 0.05$), and the blood glucose level in group A was significantly lower than that in group B after treatment ($p< 0.05$).

Comparison of serum potassium levels between group A and group B before and after treatment (B), there was no significant difference in serum and blood potassium levels between group A and group B before and after treatment (both P> 0.05). Serum and blood potassium levels in group A and group B after treatment were significantly higher than those before treatment (both $p< 0.05$), and serum potassium levels in group A after treatment were significantly higher than those in group B after treatment ($p< 0.05$).

Comparison of serum sodium levels between group A and group B before and after treatment (C), there was no significant difference in serum sodium levels between group A and group B before treatment (both P> 0.05). The blood sodium levels in group A and group B were significantly lower than those before treatment (both $p< 0.05$), and the blood sodium level of group A was significantly lower than that of group B after treatment ($p< 0.05$).

Changes of serum TNF-α, IL-6 and IL-18 concentrations before and after treatment in group A and group B

There were no significant differences in serum

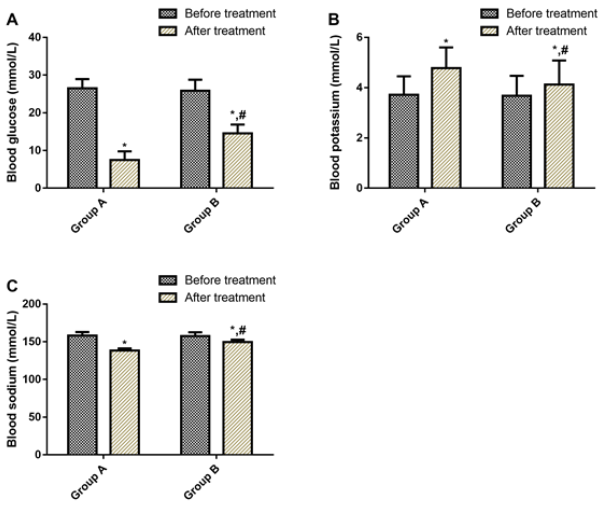

Figure 2. Comparison of blood glucose, serum potassium and blood sodium control indexes before and after treatment in group A and group B. # $p< 0.05$. Compared with before treatment, * indicated $p< 0.05$; compared with group A after treatment.

Table 4. Comparison of blood glucose, serum potassium and blood sodium control indexes before and after treatment in group A and group B ($\overline{x}$±sd).

Group	n	Blood sugar (mmol/L)		Blood potassium (mmol/L)		Blood sodium (mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group A	60	26.49±2.46	7.49±2.29*	3.72±0.73	4.78±0.82*	158.19±4.67	138.19±3.08*
Group B	62	25.85±2.92	14.54±2.36*	3.68±0.79	4.12±0.96*	157.55±4.95	149.64±3.17*
T value	-	1.298	16.610	0.288	4.049	0.729	20.070
P value	-	0.197	< 0.001	0.774	< 0.001	0.468	< 0.001

Note: Compared with before treatment, * indicated $p< 0.05$.

Table 5. Comparison of serum TNF-α, IL-6 and IL-18 levels ($\bar{x}$±sd).

Group	n	TNF-α (ng/L)		IL-6(ng/L)		IL-18(ng/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
A	60	160.95±25.34	94.95±20.47*	155.94±12.15	72.42±13.48*	668.19±48.67	309.64±45.64*
B	62	165.26±22.92	110.54±22.36*	152.88±13.69	92.64±14.96*	660.90±42.55	385.57±49.31*
T value	-	0.977	3.984	1.295	7.778	1.436	16.780
p	-	0.331	< 0.001	0.198	< 0.001	0.154	< 0.001

Note: Compared with before treatment, * indicated $p< 0.05$.

TNF-α, IL-6, and IL-18 concentrations between group A and group B before treatment (all P> 0.05). The concentrations of serum TNF-α, IL-6, and IL-18 in group A and group B were higher after treatment. The concentration of serum TNF-α, IL-6, and IL-18 in group A was significantly lower than that in group B after treatment (all $p<$ 0.05). See Table 5, Figure 3.

The serum TNF-α concentration was compared between group A and group B before and after treatment (A), and there was no significant difference between group A and group B before treatment (both $p>$ 0.05). After treatment, the serum TNF-α concentration in group A and group B decreased significantly (p <0.05). After treatment, the serum TNF-α concentration in group A was significantly lower than that in group B (p <0.05).

Serum IL-6 levels were compared between group A and group B before and after treatment (B). There was no significant difference in serum IL-6 concentration between group A and group B before treatment (all P> 0.05). Compared with before treatment, the serum IL-6 concentration in Group A and Group B was significantly reduced after treatment (both p <0.05). After treatment, the serum TNF-α concentration in group A was significantly lower than that in group B (p <0.05).

According to comparison of serum IL-18 concentration between group A and group B before and after treatment (C), there was no significant difference in serum IL-18 concentration between group A and group B before treatment (both $p>$ 0.05). Compared with before treatment, the serum IL-18 concentration in group A and group B was significantly reduced after treatment (both P <0.05). After treatment, the serum IL-18 concentration in group A was significantly lower than that in group B (p <0.05).

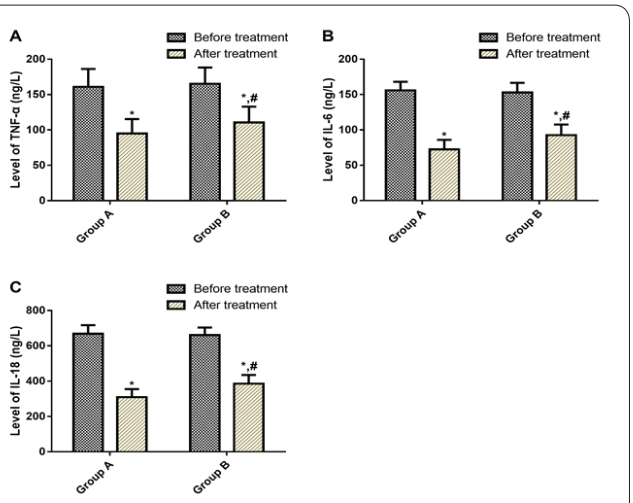

Figure 3. Changes of serum TNF-α, IL-6 and IL-18 levels before and after treatment in group A and group B, note: * indicated $p<$ 0.05, compared with before treatment; # indicated $p<$ 0.05, compared with group A after treatment.

Discussion

DKA is a common complication in children with diabetes mellitus, with increased incidence in recent years (14, 15). The incidence of DKA in children is relatively acute. If the children can be effectively rescued in time in the early stage, and the blood sugar level of the children can be decreased timely, it can be ensured that the children can safely get through the danger period (16). Therefore, effective and in-place rescue is of great significance to the prognosis quality of children with DKA (17, 18).

The key to the treatment of DKA in children is to correct acidosis, restore water, and electrolyte balance (19). In the fluid infusion and clinical practice, based on routine treatment such as correction of water and electrolyte disorders, insulin supplementation therapy for children can specifically inhibit the formation of ketone bodies and help patients effectively control the disease, and the clinical effect is remarkable (20,21). However, the grasp of insulin dose during treatment is very important (22). A study conducted by Cemeroglu et al. (23) has pointed out that adult guidelines are not suitable for children and that age should be taken into account when calculating insulin doses. Nallasamy (24) and others found that the efficacy of low-dose insulin in the treatment of children with DKA is not inferior to that of standard-dose in terms of blood sugar reduction rate and acidosis regression rate. In this study, children with DKA were treated with low-dose insulin combined with electrolyte supplementation. The results showed that the total effective rate of group A drugs was better than that of group B. After treatment, the time when blood sugar reached the standard level, the time when acidosis was corrected and the time of hospitalization in group A was significantly shorter than those in group B, and the control of blood sugar, sodium and potassium levels in group A was significantly better than that in group B. This suggests that supplementation of electrolytes in children with DKA or combination with low-dose insulin and electrolyte supplementation is a viable chemotherapy regimen, while low-dose insulin combined with electrolyte supplementation may be more effective in treating children with DKA.

Diabetes patients are often susceptible to secondary inflammatory reactions due to low self-resistance and elevated blood sugar, and infections are prone to acute complications such as DKA (25, 26). Recent studies have found that DKA is associated with increased inflammatory factors in the body (27). IL-6, IL-18,

and TNF-α are common inflammatory cytokines with multiple functions, which are considered to play an important role in DKA reaction (28-30). In this study, the concentrations of serum IL-18, IL-6, and TNF-α in group A and group B were significantly lower than those before treatment, and the serum levels of IL-18 and IL-6 in group A were significantly lower than those in group B after treatment. This suggests that low-dose insulin combined with electrolytes can improve the inflammatory response in children with DKA. In the study of Popovic et al. (31), the levels of inflammatory factors CRP and IL-6 in DKA patients after intravenous insulin therapy were significantly decreased, which is similar to our study. This suggests that low-dose insulin combined with electrolyte therapy is related to the alleviation of inflammatory response. Thus inhibiting the levels of inflammatory factors may be one of its therapeutic mechanisms (32-51).

In this study, the subjects were screened according to the exclusion and inclusion criteria. There was no significant difference in general clinical baseline data such as sex, age, and weight between groups A and B, which ensured the rigor and reliability of the study. It was confirmed that low-dose insulin combined with electrolyte supplementation had obvious benefits in the DKA application, but the risk factors of DKA in children were not observed in the study. The clinical and pathological parameters of DKA in children were different from those in other age stages. Whether low-dose insulin combined with electrolyte supplementation was suitable for DKA patients of other ages has not been explored. These shortcomings need to be further supplemented in future studies, and further evidence for the results of this study will be provided.

In conclusion, the low-dose insulin combined with electrolyte therapy is effective in children with DKA, and can effectively control blood glucose, sodium, potassium, and inflammatory cell levels, which is worthy of further clinical application.

Authors' contributions

ML W,LH F and W Z conceived and designed the study, collected, analyzed and interpreted the experiment data, drafted this paper, and revised the manuscript critically for important intellectual content. Three authors read and approved the final manuscript.

References

1. Malik FS, Hall M, Mangione-Smith R, Keren R, Mahant S, Shah SS, Srivastava R, Wilson KM, Tieder JS. Patient characteristics associated with differences in admission frequency for diabetic ketoacidosis in United States children's hospitals. J Pediatr 2016; 171: 104-110.

2. Aye T, Mazaika PK, Mauras N, Marzelli MJ, Shen H, Hershey T, Cato A, Weinzimer SA, White NH, Tsalikian E. Impact of Early Diabetic Ketoacidosis on the Developing Brain. Diabetes Care 2019; 42: 443-449.

3. Bialo SR, Agrawal S, Boney CM, Quintos JB. Rare complications of pediatric diabetic ketoacidosis. World J Diabetes 2015; 6: 167.

4. Cohen M, Leibovitz N, Shilo S, Zuckerman-Levin N, Shavit I, Shehadeh N. Subcutaneous regular insulin for the treatment of diabetic ketoacidosis in children. Pediatr Diabetes 2017; 18: 290-296.

5. Jackman J, Chafe R, Albrechtsons D, Porter R, Nugent C, Waheed S, Newhook LA. Delayed diagnosis and issues with pump usage are the leading causes of diabetic ketoacidosis in children with diabetes living in Newfoundland and Labrador, Canada. BMC Res Notes 2015; 8: 1-5.

6. Van Berkel M, Joseph J, Riha H. Successful implementation of a treatment protocol for diabetic ketoacidosis. Crit Care Med 2016; 44: 196.

7. Inward CD, Chambers TL. Fluid management in diabetic ketoacidosis. Arch Dis Child 2002; 86: 443-444.

8. Rameshkumar R, Satheesh P, Jain P. Standard dose (0.1 u/kg/hr) versus low dose (0.05 u/kg/hr) intravenous insulin infusion in the treatment of pediatric diabetic ketoacidosis randomized, double-blind controlled clinical trial. Pediatr Crit Care Med 2018; 19: 18.

9. Orwoll BE. Challenging the One-Dose-Fits-All Model for Insulin in the Acute Treatment of Pediatric Diabetic Ketoacidosis. A Critical Appraisal of "Low-Dose Versus Standard-Dose Insulin in Pediatric Diabetic Ketoacidosis: A Randomized Clinical Trial (JAMA Pediatrics 2014; 168: 999–1005.

10. Dong G, Liang L, Fu J, Zou C. Serum interleukin-18 levels are raised in diabetic ketoacidosis in Chinese children with type 1 diabetes mellitus. Indian Pediatr 2007; 44: 732-736.

11. Chen X, Wu R. Diagnostic value of TNF-alpha and IL-10 for diabetic ketoacidosis with acute pancreatitis. Int J Clin Exp Med 2018; 11: 5860-5866.

12. Kim JA, Kim DK, Jin Tae, Kang OH, Choi YA, Choi SC, Kim TH, Nah YH, Choi SJ, Kim YH. Acanthoic acid inhibits IL-8 production via MAPKs and NF-κB in a TNF-α-stimulated human intestinal epithelial cell line. Clin Chim Acta 2004; 342: 193-202.

13. Dhatariya KK, Vellanki P. Treatment of diabetic ketoacidosis (DKA)/hyperglycemic hyperosmolar state (HHS): novel advances in the management of hyperglycemic crises (UK versus USA). Curr Diab Rep 2017;17: 33.

14. Kanwal SK, Chhapola V, Kumar V. Predictors of altered sensorium at admission in children with diabetic ketoacidosis. Ind J Pediatr 2015; 82: 873-874.

15. Fazeli Farsani S, Brodovicz K, Soleymanlou N, Marquard J, Wissinger E, Maiese BA. Incidence and prevalence of diabetic ketoacidosis (DKA) among adults with type 1 diabetes mellitus (T1D): a systematic literature review. BMJ Open 2017; 7: e016587.

16. Zubair M, Mohamed NG, Al Amri M. Clinical, demographic and biochemical profile of pediatric diabetic ketoacidosis patients in King Khalid Civilian Hospital, Tabuk. Med Sci 2018; 22: 70-77.

17. Dhatariya KK, Nunney I, Higgins K, Sampson MJ, Iceton G. National survey of the management of diabetic ketoacidosis (DKA) in the UK in 2014. Diabet Med 2016; 33: 252-260.

18. Ahmed F, Kazi SG, Khan W. Type 1 diabetes mellitus presenting with diabetic ketoacidosis (DKA) in a neonate. J Pak Med Assoc 2016; 66: 1026-1028.

19. Miles JM, Gerich JE. 3Glucose and ketone body kinetics in diabetic ketoacidosis. Clin Endocrinol Metab 1983; 12: 303-319.

20. Gupta D, Kirn M, Jamkhana ZA, Lee R, Albert SG, Rollins KM. A unified Hyperglycemia and Diabetic ketoacidosis (DKA) insulin infusion protocol based on an Excel algorithm and implemented via Electronic Medical Record (EMR) in Intensive Care Units. Diabetes Metab Syndr 2017; 11: 265-271.

21. Karajgikar ND, Manroa P, Acharya R, Codario RA, Reider JA, Donihi AC, Salata RA, Korytkowski MT. Addressing pitfalls in management of diabetic ketoacidosis (DKA) with a standardized protocol 2019; 25: 407-412.

22. Kapellen T, Vogel C, Telleis D, Siekmeyer M, Kiess W. Treatment of diabetic ketoacidosis (DKA) with 2 different regimens regarding fluid substitution and insulin dosage (0.025 vs. 0.1 units/kg/h).Exp Clin Endocrinol Diabetes 2012;120: 273-276.

23. Cemeroglu AP, Thomas JP, Zande LT, Nguyen NT, Wood MA, Kleis L, Davis AT. Basal and bolus insulin requirements in children, adolescents, and young adults with type 1 diabetes mellitus on continuous subcutaneous insulin infusion (CSII): effects of age and puberty. Endocr Pract 2013;19: 805-811.
24. Nallasamy K, Jayashree M, Singhi S, Bansal A. Low-Dose vs standard-dose insulin in pediatric diabetic ketoacidosis a randomized clinical trial. JAMA Pediatr 2014; 168: 999.
25. Colino E, Álvarez MÁ, Carcavilla A, Alonso M, Ros P, Barrio R . Insulin dose adjustment when changing from multiple daily injections to continuous subcutaneous insulin infusion in the pediatric age group. Acta Diabetol 2010; 47: 1-6.
26. Mudly S, Rambiritch V, Mayet L. An Identification of the Risk Factors Implicated in Diabetic Ketoacidosis (DKA). SAFP 2007; 49.
27. Svart M, Rittig N, Møller N. Soluble CD 163 correlates with lipid metabolic adaptations in type 1 diabetes patients during ketoacidosis. J Diabetes Invest 2019; 10: 67-72.
28. Nett ST, Noble JA, Levin DL, Cvijanovich NZ, Vavilala MS, Jarvis JD, Flori HR. Biomarkers and genetics of brain injury risk in diabetic ketoacidosis: A pilot study. J Pediatr Intensive Care 2014; 03: 059-066.
29. O'Neill S, Drobatz K, Satyaraj E, Hess R. Evaluation of cytokines and hormones in dogs before and after treatment of diabetic ketoacidosis and in uncomplicated diabetes mellitus. Vet Immunol Immunopathol 2012; 148: 276-283.
30. Karavanaki K, Karanika E, Georga S, Bartzeliotou A, Tsouvalas M, Konstantopoulos I, Fotinou A, Papassotiriou I, Karayianni C. Cytokine response to diabetic ketoacidosis (DKA) in children with type 1 diabetes (T1DM). Endocr J 2011; 58: 1045-1053.
31. Popovic D, Lalic K, Jotic A, Milicic T, Bogdanovic J, Đorđevic M, Stankovic S, Jeremic V, Lalic NM. The inflammatory and hemostatic cardiovascular risk markers during acute hyperglycemic crisis in type 1 and type 2 diabetes. J Med Biochem 2019; 38: 126-133.
32. Li W, Jia MX, Wang JH, Lu JL, Deng J, Tang JX, Liu, C. Association of MMP9-1562C/T and MMP13-77A/G Polymorphisms with Non-Small Cell Lung Cancer in Southern Chinese Population. Biomolecules 2019; 9(3): 107-119.
33. Liang Y, Lin Q, Huang P, Wang Y, Li J, Zhang L, Cao J. Rice Bioactive Peptide Binding with TLR4 To Overcome H2O2-Induced Injury in Human Umbilical Vein Endothelial Cells through NF-kappa B Signaling. J Agri Food Chem 2018; 66(2): 440-448.
34. Chen HX, Huang L, Yang L, Chen YT, Huang JM. Model-based method with nonlinear ultrasonic system identification for mechanical structural health assessment. Trans Emerge Telecommun Technol 2020; 1-15.
35. Bordbar M, Darvishzadeh R, Pazhouhandeh M, Kahrizi D. An overview of genome editing methods based on endonucleases. Modern Genetics J 2020; 15(2): 75-92.
36. Chen X, Xu Y, Meng L, Chen X, Yuan L, Cai Q, Shi W, Huang G. Non-parametric partial least squares-discriminant analysis model based on sum of ranking difference algorithm for tea grade identification using electronic tongue data. Sens Actuators B Chem 2020; 311:127924-127931.
37. Guo T, Lin Q, Li X, Nie Y, Wang L, Shi L, Xu W, Hu T, Guo T, Luo F. Octacosanol Attenuates Inflammation in Both RAW264.7 Macrophages and a Mouse Model of Colitis. J Agri Food Chem 2017; 65(18): 3647-3658.
38. Jiang X, Zhu B, Chevallier J, Xie R. Allocating provincial CO2 quotas for the Chinese national carbon program. Australian J Agri Res Econ 2018; 62(3): 457-479.
39. Lou Y, Guo D, Zhang H, Song L. Effectiveness of mesenchymal stems cells cultured by hanging drop vs. conventional culturing on the repair of hypoxic-ischemic-damaged mouse brains, measured by stemness gene expression. Open Life Sci 2016; 11(1): 519-523.
40. Lou Y, Shi J, Guo D, Qureshi AK, Song L. Function of PD-L1 in antitumor immunity of glioma cells. Saudi J Biol Sci 2017; 24(4): 803-807.
41. Lou Y, Yang J, Wang L, Chen X, Xin X, Liu Y. The clinical efficacy study of treatment to Chiari malformation type I with syringomyelia under the minimally invasive surgery of resection of Submeningeal cerebellar Tonsillar Herniation and reconstruction of Cisterna magna. Saudi J Biol Sci 2019; 26(8): 1927-1931.
42. Zhang T, Wu X, Shaheen SM, Zhao Q, Liu X, Rinklebe J, Ren H. Ammonium nitrogen recovery from digestate by hydrothermal pretreatment followed by activated hydrochar sorption. Chem Eng J 2020; 379: 1-54.
43. Zhu B, Pang R, Chevallier J, Wei YM, Vo DT. Including intangible costs into the cost-of-illness approach: a method refinement illustrated based on the PM2.5 economic burden in China. Europ J Health Econ 2019; 20(4): 501-511.
44. Chen H, Chen Y, Yang L. Intelligent early structural health prognosis with nonlinear system identification for RFID signal analysis. Comput Commun 2020; 157: 150-161.
45. Yang M, Abdalrahman H, Sonia U, Mohammed A, Vestine U, Wang M, Ebadi AG, Toughani M. The application of DNA molecular markers in the study of Codonopsis species genetic variation, a review. Cell Mol Biol 2020; 2: 23-30.
46. He L, Fang H, Wang X, Wang Y, Ge H, Li C, Chen C, Wan Y, He H. The 100 most-cited articles in urological surgery: A bibliometric analysis. Int J Surg 2020; 75: 74-79.
47. Nie Y, Luo F, Lin Q. Dietary nutrition and gut microflora: A promising target for treating diseases. Trends Food Sci Technol 2018; 75: 72-80.
48. Nie Y, Luo F, Wang L, Yang T, Shi L, Li X, Shen J, Xu W, Guo T, Lin Q. Anti-hyperlipidemic effect of rice bran polysaccharide and its potential mechanism in high-fat diet mice. Food Func 2017; 8(11): 4028-4041.
49. Ren Y, Jiao X, Zhang L. Expression level of fibroblast growth factor 5 (FGF5) in the peripheral blood of primary hypertension and its clinical significance. Saudi J Biol Sci 2018; 25(3): 469-473.
50. Yaykasli KO, Yaykasli E, Ataoglu S, Ozsahin M, Memisogulları R, Çelebi E, Uçgun T, Ozcan ME, Uslu M, Yuce H. The frequency of omentin Val109Asp polymorphism and the serum level of omentin in patients with Rheumatoid Arthritis. Acta Medica Mediterranea 2013; 29:521-526.
51. Wang L, Lin Q, Yang T, Liang Y, Nie Y, Luo Y, Shen J, Fu X, Tang Y, Luo F. Oryzanol Modifies High Fat Diet-Induced Obesity, Liver Gene Expression Profile, and Inflammation Response in Mice. J Agri Food Chem 2017; 65(38): 8374-8385.