International Journal of Endorsing
HEALTH SCIENCE RESEARCH

IJEHSR

Original Article

Management of diabetic ketoacidosis: Role of Rapid Acting Insulin Analogs in comparison to regular intravenous insulin.

Ibrar Ahmed[1], Sobia Sabir Ali[1], Zafar Ali[2], Mohammad Nawaz[1] & Tahir Ghaffar[1]

[1]Department of Endocrinology, Lady Reading Hospital, Peshawar-Pakistan.
[2]Department of Medicine, Lady Reading Hospital, Peshawar-Pakistan.

Doi: 10.29052/IJEHSR.v9.i1.2021.76-82
Corresponding Author Email: drsobias@hotmail.com
Received 05/06/2020
Accepted 19/01/2021
Published 01/03/2021

OPEN ACCESS

Abstract

Background: Diabetic ketoacidosis (DKA) is an acute metabolic healthcare crisis in patients with diabetes mellitus. The current study aimed to compare the effectiveness of rapid-acting insulin analog administered subcutaneously with regular insulin infused intravenously among the DKA patients.

Methodology: In this prospective open labelled study, 100 consecutive DKA patients were randomly assigned to two groups. Group 1 patients were admitted to the intensive care unit (ICU) and treated with intravenous regular insulin infusion. Group 2 patients were managed in the emergency medical ward with subcutaneous rapid-acting insulin. Response to the therapy was assessed by the follow-up investigations of the biochemical parameters, including blood glucose concentration, serum ketones, pH, serum electrolytes including bicarbonates, sodium and potassium concentration until the resolution of DKA. Furthermore, the overall duration of therapy (blood glucose level < 250 mg/dl), time and amount of insulin administered until the resolution of DKA, were also assessed.

Results: The baseline clinical and biochemical parameters were similar between the two treatment groups except for blood glucose and sodium concentration. The mean random blood sugar (RBS), acid-base parameters and concentration of ketone bodies were significantly improved from admission until the resolution of DKA. There was no significant difference in the duration of therapy ($p=0.07$). While the time and amount of insulin therapy required until resolution of DKA were significantly reduced among the patients treated subcutaneously with rapid-acting insulin, i.e. 16.36 ± 6.92 hrs and 59.28 ± 30.05 units ($p<0.05$).

Conclusion: The patients with less complicated DKA can be managed with rapid-acting insulin analog in the medical wards obviating the need for admission to the ICU. With relatively better outcomes, it is an effective alternative to regular intravenous insulin infusion for DKA resolution.

Keywords

Diabetic Ketoacidosis, Insulin Analog, Regular Insulin, Efficacy.

Check for updates

Introduction

Diabetic ketoacidosis (DKA) is a severe life-threatening emergency condition triggered by abnormally high blood glucose concentration among patients with type 1 and type 2 diabetes. This serious metabolic derangement involves the biochemical triad of uncontrolled high blood glucose, increased ketones and metabolic acidosis. The combination of absolute or relative insulin deficiency and an increase in the release of counter-regulatory hormones like glucagon, catecholamine's, cortisol, and growth hormone result in this complication[1,2]. Type 1 diabetes patients are more prone to DKA, yet several studies suggest the patients with either type 1 or 2 diabetes are equally likely to encounter this potential threat. Nearly one-third of the DKA cases are associated with type 2 diabetes mellitus[3]. According to the most recent systematic review, a total of eight studies have reported the incidence range of 0–56 per 1000 person-years (PYs), one reported 263 per 1000 PYs and eleven studies reported 0–128 per 1000 PYs. Moreover, it was also found that the DKA prevalence decreased with increasing age[4].

Close monitoring of diabetic patients, management of electrolytic disturbances and understanding the DKA pathophysiology have resulted in a significant reduction in the overall morbidity and mortality rate associated with this public health concern. Numerous healthcare guidelines for DKA management among both children and adult diabetic patients have been formulated[5-7]. The primary treatment involves administering regular insulin via continuous intravenous infusion or frequent subcutaneous injections of rapid-acting insulin analogs[8]. However, the effectiveness of low-dose insulin therapy has been confirmed regardless of the administration route. Although the administration of continuous intravenous infusion of regular insulin preferable until the DKA resolution as the subcutaneous insulin therapy comparatively has a longer half-life and the onset of action is delayed[9,10].

As per the American Diabetes Association (ADA) recommendations for insulin administration, the treatment must encompass the transition to intermediate-acting insulin and regular insulin twice daily or multiple-dose regime of short-acting or rapid-acting and intermediate-acting or long-acting insulins[10]. The literature reports a high rate of hypoglycemic events among the patients treated with intermediate-acting and regular insulin after discontinuing intravenous insulin[11]. A review conferring the treatment modalities for DKA patients concluded that the treatment with rapid-acting insulin analogs in the non-intensive care (ICU) settings is as effective and safe as that with the intravenous infusion of regular insulin in ICU[12]. Nevertheless, the overall cost-effectiveness associated with the use of insulin analogs cannot be denied. Hence the administration of long and rapid-acting insulin analogs for glycemic control is a more practical approach to obviating intermediate-acting and regular insulin[13,14].

Considering the paucity of work and subsequent observations regarding the efficacy of subcutaneous injections of a rapid-acting insulin and intravenous insulin. The present study aimed to determine the comparative effectiveness of regular insulin and rapid-acting insulin analogs for DKA treatment.

Methodology

This prospective, open labelled study was conducted in compliance with the ethical principles of the Declaration of Helsinki at the Endocrine and Medicine Department of Lady Reading Hospital (LRH) from January to December 2018. The ethical approval was obtained from the institutional review board of LRH (Reference # 1887/MA; Dated 5-12-2017), and written informed consent was acquired from the study subjects before inclusion.

A total of 100 DKA fulfilled the inclusion criteria, i.e. patients ≥ 18 years of age (plasma glucose level > 250 mg/dl, serum bicarbonate level < 15 mmol/l, venous pH < 7.30) either diagnosed with DKA for the first time or previously diseased were recruited. While the patients with severe comorbid conditions, including myocardial infarction, end-stage renal failure, hepatic diseases, Glasgow Coma Scale (GCS) < 7, hypotension (SBP < 90

mmHg), planned for any surgical procedure and pregnant or lactating females were excluded from the study sample. Also excluded were those receiving glucocorticoids or immunosuppressive agents for known or unknown reasons.

The sample size for the study was calculated using World Health Organization (WHO) sample size determination in health studies, keeping 80% power of the test and 5% level of significance. Recruited patients were equally categorized into two groups. Subjects were randomly assigned to the treatment groups through random number sequence by Random Allocation Software version 2.0.0. After a thorough clinical assessment at the admission time, the patient's hydration status was checked based on tongue dryness, reduced skin turgor, sunken eyes, tachycardia, hypotension, and decreased urine output. The intravenous fluids were administered immediately; 0.9% of saline at 500-1000 ml/hr for 2 hrs, 0.45% of saline at 250-500 ml/hr (until blood glucose < 250 mg/dl) and dextrose 5% in 0.45% of saline at 150-250 ml/hr (until resolution of DKA). Group 1 patients (n=50) were admitted to the ICU setting, received an initial bolus of 0.1 units/kg of body weight, followed by continuous infusion of regular insulin at 0.1 units/kg/hr, which was reduced to 0.05 unit/kg/hr when the blood glucose level was < 250 mg/dl. Group 2 patients (n=50) were either managed in the general medicine ward or step down unit, received an initial subcutaneous dose of 0.3 units/kg/hr rapid-acting insulin analog, which was reduced to 0.05 unit/kg/hr when the blood glucose level was < 250 mg/dl.

The primary outcome of the study was the determination of differences in the blood glucose level (hourly), serum ketones, arterial blood gases, serum electrolytes including bicarbonates, sodium, and potassium (at 6 hrs, 12 hrs and 24 hrs) between the two groups during the treatment course. Secondary outcomes included the difference in the treatment response concerning the duration of therapy (blood glucose level < 250 mg/dl), time and amount of insulin administered among the patients of both groups until the resolution of DKA. The statistical analysis was carried out using SPSS version 22.0. Mean, and the standard deviation was used to display all continuous variables while all categorical variables were given as frequencies and percentages. Chi-square test and independent t-test were used to compare the patient baseline characteristics and the treatment outcomes between the study groups, where p-value < 0.05 was considered significant.

Results

The study included 100 DKA patients, 50 treated with regular insulin by intravenous infusion, and the remaining 50 were given rapid-acting insulin analog subcutaneously. The baseline characteristics of the patients of both groups are shown in Table 1. The baseline lab investigations were quite similar among the patients of both groups, except for the mean RBS and sodium concentrations. Group 1 patients had significantly high mean RBS levels than the group 2 patients, while the observations were inverse for the mean sodium concentration among the two groups' patients.

Table 1: Patient's characteristics on admission.

Variables		Overall (n= 100)	Group 1 Regular Insulin (n =50)	Group 2 Rapid-acting Insulin (n= 50)	p-value
Age (years)		19.82±7.70	19.42±7.50	20.22±7.95	0.60
Gender	Male	49(49.0)	26(52.0)	23(46.0)	0.58
	Female	51(51.0)	24(48.0)	27(54.0)	
Weight (kg)		43.44±12.27	43.00±13.08	43.88±11.52	0.72
Type of diabetes	Type 1	86(86.0)	45(90.0)	41(82.0)	0.25
	Type II	14(14.0)	5(10.0)	9(18.0)	

Baseline lab investigation	RBS	457.95±72.04	486.56±70.26	429.34±62.27	0.001*
	Ketones	4.31±1.48	4.51±1.48	4.12±1.48	0.19
	PH	7.14± 0.16	7.13±0.16	7.15±0.15	0.53
	Bicarbonate	13.32± 3.22	12.98±3.36	13.66±3.08	0.29
	Potassium	3.81±0.45	3.78±0.49	3.84±0.41	0.45
	Sodium	135.21±4.99	133.57±4.31	136.86±5.12	0.001*
	HbA1c	10.75±1.39	10.72±1.60	10.78±1.15	0.82
Glasgow Coma Scale*	12-15	65(65.0)	33(66.0)	32(64.0)	0.36
	7-11	33(33.0)	17(34.0)	16(32.0)	
	3-6	2(2.0)	-	2(4.0)	

Values are given as mean ± SD and n(%).
*p-value < 0.05 is considered significant.

Table 2 shows significant variations in the follow-up investigations of the biochemical parameters among the patients of both treatment groups (p<0.05).

Table 2: Follow up analysis of lab investigations in regular and rapid-acting groups.

Biochemical Parameters	Group 1-Regular Insulin (n =50)				Group 2-Rapid acting Insulin (n= 50)			
	Baseline	1st Follow up	2nd Follow up	p-value	Baseline	1st Follow up	2nd Follow up	p-value
RBS	486.56±70.26	368.10±64.52	303.24±50.94	0.001*	429.34±62.28	369.22±36.28	292.54±47.81	0.001*
Ketones	4.51±1.48	2.33±1.02	1.0±0.52	0.001*	4.12±1.48	2.29±1.37	0.73±0.41	0.001*
PH	7.13±0.16	7.26±0.10	7.34±0.07	0.001*	7.15±0.15	7.26±0.10	7.34±0.08	0.001*
Bicarbonate	12.98±3.36	17.96±2.60	23.74±2.17	0.001*	13.65±3.08	19.08±3.09	24.07±1.65	0.001*
Potassium	3.78±0.49	3.72±0.45	3.79±0.32	0.001*	3.85±0.41	3.58±0.45	3.79±0.32	0.001*

Values are given as mean ± SD.
*p-value < 0.05 is considered significant.

There was no significant difference in the duration of blood glucose decline (20.32 ± 10.96 hrs vs. 16.56 ± 9.69 hrs) between the two study groups. While the time and amount of insulin therapy required until resolution of DKA significantly varied among the patients of both groups, i.e. 74.56 ± 37.97 units vs. 59.28 ± 30.05 unit and 20.08 ± 8.00 hrs vs. 16.36 ± 6.92 hrs, respectively.

Table 3: Treatment responses among the patients of the two study groups.

Parameter	Group 1 Regular Insulin (n =50)	Group 2 Rapid-acting Insulin (n= 50)	p-value
Duration of therapy (blood glucose < 250 mg/dl) (hrs)	20.32 ± 10.96	16.56 ± 9.69	0.07
Duration of therapy until DKA resolution (hrs)	20.08 ± 8.00	16.36 ± 6.92	0.02*
Amount of insulin until DKA resolution (units)	74.56 ± 37.97	59.28 ± 30.05	0.03*

*p-value < 0.05 is considered significant.

Discussion

The local literature from Pakistan has focused on the prevalence, clinical characteristics and outcomes of DKA[15-17], but little is known regarding the therapeutic effectiveness of insulin analogs for the management of this complication. The study results showed that the administration of subcutaneous rapid-acting insulin was as effective as the treatment with intravenous infusion of regular insulin among the DKA patients. Initially, during the early treatment phase, there were no significant differences in the laboratory investigations among the two groups' patients, except for the mean RBS and sodium concentration (p=0.001). The comparable treatment response among the patients treated with rapid-acting or regular insulin for DKA resolution during this study is consistent with several previous studies indicating equal effectiveness of the two therapeutic approaches[18-20].

Both the study drugs effectively controlled the glucose concentration and improved other laboratory parameters from the first baseline investigation until DKA resolution (p<0.05). The mean blood glucose concentration and acid-base parameters at the resolution of DKA among the patients treated with rapid-acting insulin (RBS 292.54 ± 47.81 mg/dl, pH 7.34 ± 0.08, bicarbonate 24.07 ± 1.65 mmol/l) were similar to those observed among the patients treated with regular intravenous insulin (RBS 303.24 ± 50.94 mg/dl, pH 7.34 ± 0.07, bicarbonate 23.74 ± 2.17 mmol/l). Besides, we also found that ketone bodies' concentration was lower among the patients of group 2 treated with subcutaneous insulin methods than those treated with regular insulin in group 1. In support, a review including the results of five randomized controlled trials (RCTs) comparing the treatment outcomes associated with subcutaneous insulin analogs versus intravenous regular insulin infusion among DKA patients[21]. Castellanos et al. found neither the advantages nor the disadvantages between either of the treatment groups. Furthermore, Ersöz et al. and Latif et al. revealed that administration of subcutaneous insulin analogs and intravenous regular insulin infusion is equally effective for treating DKA[22,23]. Our findings differ from a prospective randomized study carried out by Fisher et al. comparing the effects of intravenous, intramuscular and subcutaneous insulin administration among DKA patients. They revealed that the blood glucose and ketone body concentration were lower, and acidosis improvements were faster among the patients treated intravenously with regular insulin than those treated intramuscularly or subcutaneously[24]. An important and interesting finding of our study was that the mean duration of treatment (20.08 ± 8.00 hrs and 16.36 ± 6.92 hrs; p=0.02) and the amount of insulin administered until resolution of DKA (74.56 ± 37.97 hrs and 59.28 ± 30.05 hrs; p=0.03) were significantly different among the patients of the two groups. Contrastingly, other studies report no statistically significant difference in terms of the amount of insulin infusion and the mean duration of treatment to resolve DKA between the two treatment groups[25,26]. While Razavi et al. reported in support of our results, they found that the amount of insulin units required until the resolution of DKA was lower among the patients treated with subcutaneous insulin analog than those treated with regular insulin[19].

Among the major limitation of the study was the small sample size. We had excluded the patients with myocardial infarction, end-stage renal failure, hepatic diseases, and hypotension. Hence, additional large prospective randomized controlled trials are recommended to address the treatment outcomes among a patient population with comorbidities. Furthermore, we had not assessed the cost-effectiveness of the two treatment approaches, as subcutaneous insulin administration tends to be more expensive. However, the dose adjustments and requirement of ICU or medical ward greatly impact the overall cost of healthcare, which needs to be investigated.

Conclusion

It is concluded from the study results that the intravenous administration of regular insulin and subcutaneous rapid-acting insulin significantly controlled the blood glucose concentration and

improved other acid-base parameters and concentration of ketone bodies. Nevertheless, the treatment with rapid-acting insulin is comparatively more effective than the regular insulin. It is associated with lower mean blood glucose concentration, significantly reduced mean duration of treatment and the amount of insulin required until DKA resolution. Hence, the subcutaneous insulin administration with better treatment outcomes obviates the need for admission in the ICU setting.

Conflicts of Interest

None.

Acknowledgement

The authors wish to acknowledge Muhammad Ahmad and Jaffer Bin Baqar from Medical Affairs department of Getz Pharma for their assistance in statistical analysis, manuscript editing and formatting.

Funding

None.

References

1. Bismuth E, Laffel L. Can we prevent diabetic ketoacidosis in children? Pediatr Diabetes. 2007;8(suppl 6):24–33.
2. White NH. Diabetic ketoacidosis in children. Endocriol Metab Clin North Am. 2000;29:657–682.
3. Wang ZH, Kihl-Selstam E, Eriksson JW. Ketoacidosis occurs in both type 1 and type 2 diabetes--a population-based study from northern Sweden. Diabet Med. 2008;25(7):867–870.
4. Farsani SF, 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(7).
5. Savage M, Kilvert A. On behalf of ABCD. ABCD guidelines for the management of hyperglycemic emergencies in adults. Pract Diabetes Inter. 2006;23:227–231.
6. Wolfsdorf JI, Craig ME, Daneman D, Dunger D, Edge JA, Lee WR. ISPAD Clinical Practice Consensus Guidelines 2009 Compendium-Diabetic Ketoacidosis in children and adolescents with diabetes. Pediatr Diabetes. 2009;10(Suppl 12):118–33.
7. New UK guidelines for DKA management from March 2010. Available at: http://www.diabetes.nhs.uk/publications_and_resources/reports_and_guidance/
8. Kitabchi AE, Umipierrez GE, Fisher JN, Murphy MB, Stentz FB. Thirty years of personal experience in hyperglycemic crises: Diabetic ketoacidosis and hyperglycemic hyperosmolar state. J Clin Endocrinol Metab. 2008;93:1541–1552.
9. Kitabchi AE, Fisher JN. Hyperglycemic crises: diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS). In Acute Endocrinology 2008 (pp. 119-147). Humana Press.
10. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes care. 2009;32(7):1335-1343.
11. Malone ML, Gennis V, Goodwin JS: Characteristics of diabetic ketoacidosis in older versus younger adults. J Am Geriatr Soc. 1992;40:1100– 1104.
12. Mazer M, Chen E. Is subcutaneous administration of rapid acting insulin as effective as intravenous insulin for treating diabetic ketoacidosis? Ann Emerg Med. 2009;53:259–263.
13. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, Hirsh IB: Management of diabetes and hyperglycemia in hospitals. Diabetes Care 2004; 27: 553– 597.
14. Inzucchi SE. Clinical practice: management of hyperglycemia in the hospital setting. N Engl J Med 2006; 355: 1903– 1911.
15. Jabbar A, Farooqui K, Habib A, Islam N, Haque N, Akhter J. Clinical characteristics and outcomes of diabetic ketoacidosis in Pakistani adults with Type 2 diabetes mellitus. Diabetic medicine. 2004;21(8):920-923.
16. Akhter J, Jabbar A, Islam N, Khan MA. Diabetic ketoacidosis in a hospital based population in Pakistan. JPMA. 1993;43(7):137.
17. Rahim M, Uddin K, Zaman S, Musa A, Rahman M, Hossain MD, Ahmed AK, Ahmed JU, Samad T, Haque HF, Dewan P. Clinical spectrum and management of diabetic ketoacidosis: experience in a tertiary care hospital. Birdem Med J. 2011;1(1):15-20.
18. Umpierrez GE, Jones S, Smiley D, Mulligan P, Keyler T, Temponi A, Semakula C, Umpierrez D, Peng L, Cerón M, Robalino G. Insulin analogs versus human insulin in the treatment of patients with diabetic ketoacidosis: a randomized controlled trial. Diabetes care. 2009;32(7):1164-1169.
19. Razavi Z, Maher S, Fredmal J. Comparison of subcutaneous insulin aspart and intravenous

regular insulin for the treatment of mild and moderate diabetic ketoacidosis in pediatric patients. Endocrine. 2018;61(2):267-274.
20. Karoli R, Fatima J, Salman T, Sandhu S, Shankar R. Managing diabetic ketoacidosis in non-intensive care unit setting: role of insulin analogs. Indian J pharmacology. 2011;43(4):398.
21. Andrade - Castellanos CA, Colunga - Lozano LE, Delgado - Figueroa N, Gonzalez - Padilla DA. Subcutaneous rapid - acting insulin analogues for diabetic ketoacidosis. Cochrane Database of Systematic Reviews. 2016(1).
22. Ersöz HÖ, Ukinc KU, Köse M, Erem C, Gunduz A, Hacihasanoglu AB, Karti SS. Subcutaneous lispro and intravenous regular insulin treatments are equally effective and safe for the treatment of mild and moderate diabetic ketoacidosis in adult patients. Int. J. Clin. Pract. 2006;60(4):429-433.
23. Latif K, Umpierrez G, Stoever J, Blaho K, Freire A, Parks L, Culbreath B, Kitabchi A. Subcutaneous lispro insulin in the treatment of diabetic ketoacidosis. Diabetes. 2002;51.
24. Fisher JN, Shahshahani MN, Kitabchi AE. Diabetic ketoacidosis: low-dose insulin therapy by various routes. N. Engl. J. Med. 297(5):238-241.
25. Cohn BG, Keim SM, Watkins JW, Camargo CA. Does management of diabetic ketoacidosis with subcutaneous rapid-acting insulin reduce the need for intensive care unit admission? J. Emerg. Med. 49(4):530-538.
26. Umpierrez GE, Cuervo R, Karabell A, Latif K, Freire AX, Kitabchi AE. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. Diabetes care. 2004;27(8):1873-1878.