Original Article

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The Study of Different Clinical Pattern of Diabetic Ketoacidosis and Common Precipitating Events and Independent Mortality Factors

Internal Medicine Section

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ABSTRACT

Introduction: Diabetic Ketoacidosis (DKA) is an important cause of morbidity and mortality among diabetic patients in spite of major advances in the pathogenesis and more standardized diagnosis and treatment.

Aim: To find out the different patterns of clinical presentations, common precipitating factors and independent mortality factors in DKA.

Materials and Methods: This study was conducted in a tertiary care hospital, Mysuru on 110 patients from November 2007 to October 2009. Clinical presentation and precipitating factors of DKA were monitored.

Univariate analysis was done to identify statistically significant risk factors contributing to DKA mortality and was used for multiple logistic regressions to identify independent mortality predictors. A scoring methodology was used to identify the risk of having multiple risk factors in an individual.

Results: In this study, the mean age was 42.33 years, with a male to female ratio of 1.2:1. The most common complaints were vomiting and generalized weakness seen in 55 (50%) and 49 (44.5%) cases respectively. The most common precipitating factors were infections and poor compliance to antidiabetic treatment seen in 57 (52%) and 23 (21%) cases respectively. The predictors of mortality included age equal to or more than 65 years, Depressed Mental State (DMS) in the first 24 hour, insulin requirement equal to or more than 50 units in the 12 hours to bring blood glucose to less than 300 mg%, fever in the first 24 hours, shock in the first 24 hours, RBS persistently equal to or more than 300 mg% even after 12 hours with standard treatment protocol, fluid requirement equal to or more than 6 L in the first 24 hours, pH less than 7.2 and bicarbonate less than 15 mmol/l at presentation were statistically significant predictors of mortality. Multivariate analysis failed to identify an independent mortality factor; but, adverse parameters of more than 5 was significantly associated with death.

Conclusion: Risk stratification of patients with DKA is possible from simple clinical and laboratory variables available during the first day of hospitalization and further channeling the patients to ICU at the correct time to prevent mortalities.

Keywords: Clinical presentation, Diabetic acidosis, Precipitating factors, Risk factors

INTRODUCTION

Diabetic Ketoacidosis (DKA) continues to be an important cause of morbidity and mortality among patients with diabetes, in spite of major advances in the understanding of its pathogenesis and standard protocol in the diagnosis and treatment. Between 1996 to 2006, there was 35% increase in the number of cases, with a total of 136,510 cases with a primary diagnosis of DKA in 2006 [1].

Currently, 4%-9% of diabetic patients are admitted with DKA [2]. One of the study from Rhode Island showed that cost of treatment of DKA for one year was estimated to be $225 million [3]. It was reported that treatment of DKA episodes represents more than one-fourth of direct medical care for adult patients with type 1 diabetes and for half of that is spent on treating multiple episodes of ketoacidosis [4]. The estimated annual mean medical care charges of DKA in US is —$13,000 per patient per episode, yearly hospital cost for patients with DKA may exceed $1 billion [2,5].

Mortality rate, which is less than 5% in DKA, increases substantially with aging due to the presence of concomitant life-threatening illness [2]. Similar outcomes of treatment of DKA have been noted in both community and teaching hospitals [6,7]. The outcome of the treatment is not dependent on the treating physician, as long as standard protocols are followed [8].

No standard criteria for determining the severity of DKA exist in literature. Besides, data on prediction of mortality from DKA is also lacking. However, few retrospective studies have been published addressing the issue of ICU admission criteria for DKA [9,10].

This study was done to assess the value of clinical and laboratory parameters available during the first 24 hours of hospitalization in the prediction of mortality in patients presenting with DKA.

Evaluation of such parameters will aid in identifying DKA patients at risk of increased mortality, and thus manage appropriately.

MATERIALS AND METHODS

It was a prospective study. All patients having known or unknown diabetes hospitalized at JSS Medical College Hospital, Mysuru, Karnataka, India with a diagnosis of DKA (blood glucose more than 250 mg/dl, arterial pH less than 7.3, bicarbonate less than 15 mEq/L and moderate degree of ketonuria) during the period November 2007 to October 2009 were recruited for the study. Total 110 patients admitted with the above diagnosis were recruited and completely evaluated, in whom standard protocol was followed for treatment of DKA. Ethical clearance was given by the Ethical Committee of JSS Medical College, Mysuru. Informed consent was taken by the subjects and attendants in case of unconscious patients.

Pregnant women, patients with pre-existing chronic illnesses like Congestive Cardiac Failure (CCF), liver & renal impairment, type 2 respiratory failure and those not treated according to standard protocol were excluded.

Total WBC count, blood urea, serum creatinine, serum sodium, serum potassium, arterial blood pH, arterial blood bicarbonates (HCO_3), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), serum total bilirubin, other routine and relevant investigations were noted in search of precipitating factors.

Presence of DMS, defined as any level of sensorium other than fully conscious and oriented, pulse rate, blood pressure, body temperature, capillary blood glucose, units of regular insulin administered, litres of normal saline administered and urine output were noted.

A master chart was prepared using the following parameters like presenting symptoms and precipitating and mortality factors like age more or less than 65 years, presence or absence of fever (defined as temperature above 98.9°F in the morning and 99.9°F in the evening), DMS. (This included drowsy, delirious, obtunded, stuporous, semi-comatose and comatose patients). Shock (defined as blood pressure <90 mm of Hg systolic + pulse rate >100 beats per minute + urine output less than 0.5 ml/kg/hour), RBS (more or less than 300 mg/dL after 12 hours after treatment using standard protocol, blood pH more or less than 7.2, blood HCO_3 more or less than 15 mmol/L, blood Urea more or less than to 100 mg%, serum creatinine more or less than to 1.6 mg%, serum sodium more or less than to 150 meq/l, serum potassium more or less than to 3.5 meql/l, total WBC count more or less than to 15,000/mm^3, Fluid requirement more or less than 6 litres in 24 hours, serum bilirubin more than or less than 1.5 mg%, ALT and AST more or less than 80 IU, insulin requirement more or less than 50 units in 12 hours to bring serum glucose to less than 300 mg%.

STATISTICAL ANALYSIS

The data in the proforma of all the 110 patients enrolled in the study was entered into the EPINFO version 7.0.5 software. A p-value less than 0.05 was considered as statistically significant. Less than 0.01 was considered as very significant and less than 0.001 was considered as very highly significant.

Scoring methodology was used to identify the association between the number of statistically significant adverse variables present in an individual and the outcome. A score was defined as number of adverse parameters presenting in an individual in the first 24 hours. A cut off score (i.e., the number of adverse parameters identified) of 5 was utilized to study the association with death as outcome. A similar scoring system was followed by Esjtathiou SP et al., [11].

Multiple logistic regression analysis was done using all variables with p-value <0.5 after univariate analysis to find out the variables which are independent predictors of mortality in DKA.

RESULTS

The average age was 42.33 years, with 90 patients (81.81%) less than 65 years. There were 60 males (54.54%) with male: female ratio of 1.2: 1. Out of 110 patients with DKA, 10 patients died, with the mortality rate in the hospital being 9.09%. The most common presenting symptom was found to be vomiting seen in almost 50% (55 cases) of individuals, followed by generalized weakness and abdominal pain. The details of other symptoms are mentioned in [Table/Fig-1].

Precipitating Factors

The most common precipitating factor in our study was found to be infections which accounted for 52% (57 cases). Other causes like stroke, binge alcohol and emotional disturbances were seen in 2.7% of cases. In 10% (11 cases) cases no cause could be recognized in spite of search for common precipitants through proper history, clinical examination and lab investigation. Details are in [Table/Fig-2].

Symptoms	No. of Patients	Percentage
Vomiting	55	50%
Fever	39	36%
Pain abdomen	46	42%
Generalized weakness	49	44.5%
Pain, swelling and redness of skin (cellulitis)	16	14.5%
Polyuria/polydipsia/polyphagia	37	34%
Breathlessness	21	19%
Depressed mental state	31	28%
Others	44	40%

[Table/Fig-1]: Percentage distribution of patients according to symptoms.

Among the infections, Urinary Tract Infection (UTI) was seen in 27% of cases. The details of the rest of the infections are mentioned in [Table/Fig-3].

Precipitating factors	No. of Patients	Percentage
Infection	57	52%
Skipped anti-diabetic treatment	23	21%
Newly detected diabetes	12	11%
Cardiovascular diseases	4	3.6%
Others	3	2.7%
Unknown causes	11	10%

[Table/Fig-2]: Percentage distribution of patients according to precipitating factors.

Infections	No. of Patients	Percentage
Urinary tract infections	15	27%
Respiratory tract infections	12	21%
Cellulitis	14	24%
Acute gastroenteritis	8	14%
Other infections	8	14%

[Table/Fig-3]: Percentage distribution of patients according to type of infections.

Predictors of Mortality

At the end of univariate analysis the following statistically significant variables were identified as probable predictors of mortality:

1. Age more than 65 years of age, DMS in the first 24 hours, insulin requirement in the first 12 hours more than 50 units to reduce RBS to less than 300 mg%. All had very high statistical significance (p-value<0.001) in predicting mortality among DKA. These are mentioned in the [Table/Fig-4-6];
2. Fever in the first 24 hours, shock in the first 24 hours, RBS persistently more than 300 mg% even after 12 hours with standard treatment protocol and fluid requirement more than 6 L in the first 24 hours were found to be statistically very significant (p-value<0.01) in predicting mortality in DKA [Table/Fig-7-10];
3. pH less than 7.2 at presentation and bicarbonate less than 15 mmol/l were found to be just statistically significant (p-value <0.05) in predicting mortality in DKA [Table/Fig-11,12].
4. Rest of the parameters like urea, creatinine, serum sodium, serum potassium, total count, serum bilirubin, AST and ALT were not statistically significant in predicting mortality in DKA.

A scoring methodology was adopted to study the association of the statistically significant adverse parameters in a particular individual with DKA with mortality as mentioned in [Table/Fig-13].

There were eight patients out of 14 (57.14%) who had a score of more than 5. All of them died, which was statistically highly significant with a p-value of 0.001.

Multiple logistic regressions analysis was done using EPINFO software on statistically significant univariate factors to identify the

Age	Outcome				Odd's ratio	p-value
	Alive		Dead			
	Count	Percent	Count	Percent		
<65 years	85	94.4%	5	5.6%	5.667	0.006
>/- 65 years	15	75%	5	25%		

[Table/Fig-4]: Percentage distribution of patients based on outcome and age.

DMS in first 24 hours	Outcome				Odd's ratio	p-value
	Alive		Dead			
	Count	Percent	Count	Percent		
Absent	75	98.7%	1	1.3%	27.000	0.001
Present	25	73.5%	9	26.5%		

[Table/Fig-5]: Percentage distribution of patients based on outcome and DMS.

Insulin required to decrease RBS to < 300 mg%	Outcome				Odd's ratio	p-value
	Alive		Dead			
	Count	Percent	Count	Percent		
< 50U	65	98.5%	1	1.5%	16.714	0.001
>/- 50U	35	79.5%	9	20.5%		

[Table/Fig-6]: Percentage distribution of patients based on outcome and insulin requirement in 12 hour.

Fever in first 24 hours	Outcome				Odd's ratio	p-value
	Alive		Dead			
	Count	Percent	Count	Percent		
Absent	73	97.3%	2	2.7%	10.815	0.002
Present	27	77.1%	8	22.9%		

[Table/Fig-7]: Percentage distribution of patients based on outcome and fever.

Shock in the first 24 hrs.	Outcome				Odd's ratio	p-value
	Alive		Dead			
	Count	Percent	Count	Percent		
Absent	73	96.1%	3	3.9%	6.309	0.009
Present	27	79.4%	7	20.6%		

[Table/Fig-8]: Percentage distribution of patients based on outcome and shock.

RBS after 12 hours	Outcome				Odd's ratio	p-value
	Alive		Dead			
	Count	Percent	Count	Percent		
< 300 mg%	72	97.3%	2	2.7%	10.286	0.002
>/-300 mg%	28	77.8%	8	22.2%		

[Table/Fig-9]: Percentage distribution of patients based on outcome and RBS.

Fluid requirement >6 L n 24 hours	Outcome				Odd's ratio	p-value
	Alive		Dead			
	Count	Percent	Count	Percent		
< 6 L	73	97.3%	2	2.7%	10.81 (2.2-54)	0.002
>/-6 L	27	77.1%	8	22.85%		

[Table/Fig-10]: Percentage distribution of patients based on outcome and fluid in 24 hours.

pH at pre-sentation	Outcome				Odd's ratio	p-value
	Alive		Dead			
	Count	Percent	Count	Percent		
>7.2	65	97%	2	3%	7.429	0.013
</-7.2	35	81.4%	8	18.60%		

[Table/Fig-11]: Percentage distribution of patients based on outcome and pH.

independent factors associated with outcome. Results indicated that no factor stood independently associated with DKA mortality. This clearly indicates each factor has relation with other factors in explaining the variation in the outcome.

HCO3 at pre-sentation	Outcome				Odd's ratio	p-value
	Alive		Dead			
	Count	Percent	Count	Percent		
>15mmol/l	60	96.8%	2	3.2%	6.000	0.02
</-15mmol/l	40	83.3%	8	16.7%		

[Table/Fig-12]: Percentage distribution of patients based on outcome and HCO_3.

Adverse parameters present in each individuals (Score)	Total no. of individuals in each group	Living	Expired
Zero	10	10	0
One	22	22	0
Two	25	25	0
Three	18	18	0
Four	11	10	1
Five	10	9	1
Six	4	3	1
Seven	5	3	2
Eight	4	0	4
Nine	1	0	1

[Table/Fig-13]: Number of individuals under each score.

DISCUSSION

The average age of patients admitted with DKA is between 40 to 50 years [12-14] with male to female ratio of 1:1 to 1.4:1 [15-17]. In this study the average age was 42.33 years, with 81.81% less than 65 years and male: female ratio being 1.2:1.

The mortality rate in patients with DKA is less than 5% in experienced centers, 5%-15% in community hospitals and 30% of all intensive care cases [11,17]. In this study, the hospital mortality rate was 9.09%.

Usually DKA most commonly presents with nausea and vomiting, polyuria and polydypsia, abdominal pain and dizziness and altered sensorium [16-19].

In this study, the most common presenting symptom was found to be vomiting, seen in almost 50% of individuals, followed by generalized weakness, abdominal pain, symptoms of hyperglycaemia, fever, DMS and breathlessness.

Precipitating factors of DKA in the descending order of frequency includes infections (52%), skipping of anti diabetic treatment (21%), undiagnosed diabetes (11%). Among infections, urinary tract infection is the commonest (27%) followed by cellulitis and respiratory infections. In most of the studies, the precipitating factors are infection, skipping of medication, undiagnosed diabetes and comorbid conditions [14-17,20,21]. The earlier studies showing various precipitating factors in DKA are shown in [Table/Fig-14] [12,22-26].

Old age is an independent mortality predictor of DKA [17,19]. In this study 25% of patients with more than 65 years died with a p-value of 0.006 which is statistically very significant.

Fever in DKA is primarily due to the precipitating factor or due to elevated counter regulatory hormones [27]. Fever in the first 24 hours of onset of DKA is an independent risk factor for mortality in DKA [27]. In this study, 31.81% of the patients had fever, out of which 22.9% expired with a p-value of <0.002 which is statistically very significant.

DMS depends on extent of dehydration, presence of co morbid diseases; type of precipitating factor [27]. Presence of this variable at presentation or within first 24 hours is an independent risk factor for mortality in DKA [28,29]. In this study, 28% of the patients had

Study location /References	Number of episodes	Infections	Concomitant cardiovascular disease	Inadequate insulin treatment or noncompliance	New onset	Other medical illness	Unknown
Frankfurt, Germany / Petzold R et al., [22]	472	19	5	38	+	+	+
Birmingham, U.K./1968-1972/ Soler NG et al., [23]	258	28	3	23	+	+	+
Erfurt, Germany/1970-1971/ Panzram G [24]	133	35	4	21	+	+	+
Basel, Switzerland / 1968 -1978/ Berger W et al., [25]	152	43	-	26	+	+	+
Memphis, TN / 1974-1985/ Kitabchi AE et al., [12]	202	38	-	28	22	10	4
Atlanta GA / l993-1994/Umpierrez GE et al., [26]	144	28	-	41	17	10	4

[Table/Fig-14]: The earlier studies showing various precipitating factors in DKA [12,22-26].

DMS in the first 24 hours, out of which 26.5% expired with a p-value of 0.001, which is statistically very highly significant.

Shock in DKA is primarily hypovolemic resulting from severe osmotic diuresis as a result of glycosuria and also due to loss of water through hyper ventilation [30]. Our study showed that 30.9% of patients had shock in the first 24 hours, out of which 20.6% expired with a p-value of 0.01. Presence of shock was found to be a statistically significant predictor of mortality.

None of the earlier studies have shown shock as significant predictor of mortality in DKA, probably because in the earlier studies all co morbidities were included which might have contributed to death nullifying the effect of shock as a mortality predictor.

Glucose more than 300 mg/dL after 12 hour of standard protocol treatment is an independent risk factor for mortality [11].

In this study, patients with RBS more than 300 mg% at or after the first 12 hours were 32.7% of which 22.2% had resistant RBS and expired. A p-value was found to be 0.002 which is statistically very significant.

The degree of acidosis was assumed to be a predictor of mortality and was statistically proven as an independent mortality predictor [11]. In this study, patients with severe acidosis had increased mortality rates. 39.09% of the patient had pH less than 7.2, of which 18.6% expired with a p-value of 0.013, which is statistically significant.

In this study, 43.6% cases had HCO_3 less than 15 mmol/L, of which 16.7% expired. 3.2% of the patients with HCO_3 more than 15 mol/l expired. The p-value was found to be 0.02 and statistically just significant. This is similar to a study done by Trikia S et al., where mortality was high in patients who had a low bicarbonate level [17]. But in another study, the effect of HCO_3 was not significant [11].

Insulin requirement is dependent on presence of precipitating or stress factor and dehydration [29]. Mortality prediction studies showed that the administration of more than 50 units of regular insulin within first 12 hours is itself an independent predictor of mortality [11].

The insulin requirement in the first 24 hours was more than 50 units in 40% of patients, out of which 20.5% expired. A p-value was found to be 0.001 which is a very significant predictor of mortality.

Fluid requirement more than 6 litres in 24 hours is a significant predictor of mortality as per mortality prediction studies [11]. In this study, 31.8% of patients required fluids more than 6 litres in 24 hours, of which, 22.9% expired. The p-value was found to be 0.002 which is statistically a very significant predictor of mortality.

Other parameters at admissions like serum sodium, serum potassium, blood urea, serum creatinine, total WBC count, serum bilirubin, AST and ALT were shown to have no statistically significant values in predicting mortality in DKA which is being further supported by earlier studies [11].

It was observed that patients with adverse parameters more than five died in our study. Statistically very high significant association was observed with eight patients dying in this group with a p-value of 0.001. This is similar to the study done by Efstathiou SP et.al, where the mortality was high in cases where the independent predictors were more than 5 [11].

LIMITATION

The main limitation of this study is the small number of patients recruited for the study. Similar type of studies can be conducted in a larger group, may be multicentric, which will help in the risk stratification of patients with DKA at the time of admission.

CONCLUSION

The most common presenting complaints in DKA are vomiting and generalized weakness. The most common precipitating factors are infection and non-compliance to anti diabetic treatment. On the first day of hospitalization risk stratification of patients with DKA is possible from simple clinical and laboratory variables. Patients with higher score of adverse parameters, especially more than 5 are more prone for mortality and such patients need to be monitored carefully to prevent such outcomes.

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