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A STUDY OF CLINICAL PROFILE, COMPLICATIONS AND OUTCOME OF DIABETIC KETOACIDOSIS AND ASSOCIATED CO-MORBIDITIES IN A TERTIARY CARE CENTRE IN CENTRAL INDIA

Paediatrics

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ABSTRACT

Background: Diabetes is one of the largest global public health concerns, imposing a heavy global burden on the health of individuals. Uncontrolled diabetes mellitus can lead to precipitation of severe life threatening complication of Diabetic ketoacidosis (DKA), which affects one-third of the patients of T1DM.1 If these symptoms are not evaluated and treated promptly, it can become a medical emergency. The aim of the research was to study the clinical profile and outcome of children with diabetic ketoacidosis in a tertiary care centre in Central India. **Methods:** This descriptive study was conducted in pediatric ICU of a tertiary level care hospital at Indore, Madhya Pradesh for one year study period (Oct 2020-Sept 2021). Thirty children admitted with DKA were enrolled in the study and information with respect to the personal details, clinical features, laboratory parameters, management and outcome was recorded using a predesigned proforma. The data was analyzed using SPSS software. **Results:** The mean age at presentation was 9.8 years (range: 16 months -14 years) with a male:female ratio of 1.4. Sixty six percent were already diagnosed cases of type 1 DM, now presenting as DKA. Seventy three percent patients presented with severe DKA. The most common presenting complaints were fever and polyuria and polydipsia in 73% cases. The mean length of DKA resolution was 17.1 hours. The mortality rate was 3.3% (1 case). **Conclusions:** Diabetic ketoacidosis is a life threatening complication of diabetes mellitus in children. Early identification and careful monitoring of fluids, electrolytes and renal function are the cornerstones of successful DKA management.

KEYWORDS

DKA, T1DM, Cerebral oedema.

INTRODUCTION

Diabetic ketoacidosis (DKA) is considered to be a life threatening presentation of type 1 diabetes mellitus in children. It constitutes a medical emergency with significant morbidity and mortality. It is found that at places with less developed medical facilities, the risk of death from DKA is greater. Overall mortality in children with DKA varies from 3.4% to 13.4% in developing countries like India, Pakistan and Bangladesh [2]. DKA is the result of a critical relative or absolute deficiency of insulin, resulting in intracellular starvation of insulin-dependent tissues (muscle, liver, adipose). There is associated release of the counter-regulatory hormones namely, glucagon, catecholamine, cortisol and growth hormone.

The presenting complaints in DKA patients maybe polydipsia, polyuria, weight loss, fatigue, lack of concentration or recurrent infections. Abdominal pain, nausea, and vomiting are also common presenting complaints. The other findings include confusion, drowsiness, progressive, depressed mental status and eventually loss of consciousness.

The biochemical criteria for DKA diagnosis include hyperglycemia (blood glucose [BG] higher than 11 mmol/L or ≥200 mg/dL) with a venous pH of <7.3 and/or a bicarbonate (HCO3) level of <15 mmol/L; ketonemia and ketonuria.

The severity of DKA is categorized by the degree of acidosis: Mild DKA is characterized by a venous pH of <7.3 and/or a HCO3 level of <15 mmol/L, moderate DKA is characterized by a venous pH of <7.2 and/or a HCO3 level of <10 mmol/L and in severe DKA, venous pH is <7.1 with or without a HCO3 level <5 mmol/L.

High index of clinical suspicion is essential for early diagnosis and proper intervention. The important principles of DKA treatment include careful replacement of fluid deficits, correction of dehydration, correcting acidosis and hyperglycemia via insulin administration, maintaining blood glucose levels at a normal range, correcting electrolyte imbalance and treatment of any precipitating cause.

Cerebral edema is the most important complication of DKA. It is associated with a high mortality rate of 20 to 90 %. Cerebral edema is primarily a clinical diagnosis and should be suspected when there is an unexpected deterioration in neurological status after initial improvement or persistence of a comatose state without an obvious cause.

Excellent diabetes control is extremely crucial in long term management of T1DM. The specific components of therapy include initiation and adjustment of insulin, extensive teaching of the child and caretakers, and re-establishment of the life routines.

MATERIALS AND METHODS

This prospective observational study was conducted at a Tertiary care hospital in Indore, Madhya Pradesh , over a period of 12 months (Oct 2020- Sept 2021) after clearance from the Institutional Ethics Committee. The Pediatric ICU is 10 bedded medical facility with provisions for with mechanical ventilation. All the patients presenting with DKA during 1 year of study period were included in this study and as a result 30 patients were enrolled in our study.

Inclusion Criteria: All children (≤18 years) newly diagnosed or known cases of diabetes mellitus presenting with features of diabetic ketoacidosis were included in the study.

Baseline data including demographics, presenting symptoms and signs at the time of admission along with precipitating factors like inter-current illnesses, laboratory parameters, management, complications and outcome were recorded in a predesigned proforma.

As part of the management , intravenous fluid and insulin infusion was initially administered. We followed Milwaukee regimen for the treatment of DKA. Diabetic ketoacidosis was diagnosed when :

- the blood sugar at admission was >200 mg/dl
- acidosis <pH 7.3,
- plasma bicarbonate <15 mmol/L .[3]

Hyponatremia and hypernatremia was defined as values, <135 mEq/L and >145 mEq/L respectively. Similarly, hypokalemia and hyperkalemia was defined as values, <3.5 mEq/L and >5.5 mEq/L respectively.

All patients were monitored every hour for clinical features (heart rate, respiratory rate, blood pressure, urine output, oxygen saturation, sensorium, headache, vomiting) and every 2 hours for blood sugar level. Arterial/venous blood gas analysis, serum electrolytes and renal function test were measured and blood culture was done in case of suspected sepsis.

Shock was defined as tachycardia and signs of poor end-organ perfusion as defined by poor peripheral pulses, prolonged capillary

refill or flash refill, altered sensorium, cold extremities and decreased urine output.Cerebral edema was diagnosed as per the diagnostic criteria as suggested in Muir et al study.[4] This criteria includes-Abnormal motor or verbal response to pain, decorticate or decerebrate posture, cranial nerve palsy (especially 3, 4, 6), abnormal neurogenic respiratory pattern (grunting, tachypnea, Cheyne-Stokes respiration, apneusis).

Once the ketoacidosis resolved and the condition of the patients stabilized, the insulin infusion was transitioned to subcutaneous insulin. The insulin infusion was stopped when the children were alert, able to tolerate oral feeds and were metabolically stable (blood pH >7.3, plasma bicarbonate >15 mmol/L). Regular insulin (according the weight and age in 4 divided doses) was administered 1 hour before stopping the insulin infusion. Regular insulin was replaced with mixed insulin (30/70) once the blood sugar had stabilized. Potassium replacement/restriction was given as required.

Statistical Analysis

Data collected was entered in Excel format and analyzed using SPSS software. The qualitative variables were expressed as number or percentage. Descriptive data were analyzed with statistical test like mean and standard deviation. Associations were evaluated using Chi-square test, likelihood ratio and Fisher's exact test. A p value of <0.05 is considered statistically significant.

RESULTS

A total of 30 patients were included in the study. The age of the patients ranged from 16 months to 14 years old. The number of DKA patients in 1-5 yrs , 6-10 yrs and 11-14 yrs were 4, 10 and 16 respectively, and the mean age of presentation was 9.8 years with the most common age group being 11-14 years.The male to female ratio was 1: 4 with females being 80% (n=24) of all the patients.

Out of the total DKA admissions, 19 patients (63.3%) were known cases of T1DM presenting with DKA while 11 patients (36.7%) of DKA were newly diagnosed cases of T1DM. Majority of the patients presented with severe DKA (73.3%) whereas mild and moderate DKA were found in 20% and 6% patients respectively.

Table 1: Severity of DKA

Severity of DKA	Frequency	Percentage (%)
Mild	6	20.0
Moderate	2	6.7
Severe	22	73.3
Total	30	100.0

Family history of diabetes mellitus was present in 2 children (6%) in 1st degree relatives. Demographic variables like age (p value - 0.581), gender (p value - 0.824), previous status of Type 1 Diabetes Mellitus (p value -1.212) did not have any significant association with the severity of DKA.

80% of the patients(n=24) were managed in ICU, whereas 20% patients(n=6) were managed in the wards. Out of already diagnosed cases of T1DM (n=19), only 1 patient was on intensive insulin therapy (5.2%), rest 94.8% patients (n=18) were on conventional insulin therapy (Mixtard insulin).

Table 2 : Demographic characteristics of patient presenting with DKA

Characteristics	Frequency (n)	Percentage (%)
Gender		
Male	6	20
Female	24	80
Age (years)		
1-5	4	13.3
6-10	10	33.3
11-14	16	53.3
Admission		
PICU	24	80
WARD	6	20
Time of diagnosis of Diabetes		
1st episode	11	36.7
Diagnosed	19	63.3
Type of Insulin treatment		
Mixtard	18	94.8
Glargine + short acting (Regular Insulin)	1	5.2

The major recognized precipitating factors was found to be infection73% of the patients (n=23). In already diagnosed patients of type 1 DM, now presenting as DKA; infection was seen in 57.8%, inadequate insulin therapy was present in 42.3 % percent patients and missed dose of insulin was found in 31%.

Table 3 : Precipitating factors of DKA

Parameter	Frequency (n)	Percentage (%)
Infection	23	73
Insufficient Insulin therapy	8	42.3
Missed dose of insulin	6	31
Unknown	13	43

In the current study, the most common presenting symptom was found to be fever along with polyuria and polydipsia seen in 73% of individuals respectively, followed by vomiting and fast breathing (63%). Clinical presentation was analyzed and it was found that pain abdomen and malaise was present in 60% of the patients (n=18) and depressed mental status was present in 56% of cases (n=17) respectively.Tachypnea and shock at the time of admission was found in 76% patients whereas dehydration and altered sensorium was seen in 66% and 63% of the patients respectively. Kussmaul's breathing was present in 13% of the patients.

Table 4 : Initial clinical presentation of patients presenting with DKA

Characteristics	Frequency	Percentage(%)
Fever	22	73.3
Polyuria and Polydipsia	22	73.3
Vomiting	19	63.3
Fast breathing	19	63.3
Malaise	18	60.0
Pain Abdomen	18	60.0
Depressed mental status	17	56.7
Cellulitis	2	6.7

The mean pH at the time of admission and after 12 hours and 24 hours was 6.93±0.12, 7.14±0.09 and 7.33±0.06 respectively. The mean pCO2, HCO3 was 12.39±3.16 and 6.16±2.09 respectively. The mean blood glucose of 15 patients which were recorded with a glucometer was found to be 420mg/dl and in rest 15 patients the glucose reading was recorded as HI. While 43% of the patients had hyponatremia at the time of presentation, 20% of the patients were found to have hypokalemia. Blood cultures were positive only for 4 patients.

Table 5 : Laboratory parameters of patients presenting with DKA

LAB PARAMETERS	MEAN VALUES
Blood sugar (mg/dl)	420
pH (at admission)	6.93
pCO2 (at admission)	12.39
HCO3 (mmol/L)	6.16
Serum Na (mmol/L)	132.89
Serum K (mmol/L)	3.99
Serum urea (mg/dL)	45.52
Serum creatinine (mg/dL)	0.99
Hemoglobin (g/dL)	11.59
Total leukocyte counts	16000
HbA1C	13.21

Intravenous fluid, oxygen inhalation and insulin infusion was required in 73% (n=22), 70% (n=21) and 80% (n=24) of the patients respectively. Out of all the patients with severe DKA, only (13%) required more than 1 bolus and only 2 patients (6%) had to be started on ionotropic support. Continuous insulin infusion was required in 24 patients (80%) who presented with DKA in the acute phase whereas 6 patients (20%) were managed directly with subcutaneous insulin. HCO3 therapy was not given to any patient in our study. Only 1 patient (3%) required mechanical ventilation.

The major complication was found to be shock as seen in 73.3% of the patients. Other complications like cerebral edema and renal failure were observed in 13.3% and 10% of the patients. Out of total patients admitted with DKA, 29 patients were discharged and 1 patient died due to concomitant Pulmonary Tuberculosis. 6% (n=2) patients had hypothyroidism associated with type 1 Diabetes Mellitus.

Table 6 : Association of Clinical Parameters with Severity of Diabetic Ketoacidosis

Signs	Mild/Moderate	Severe	P value
Tachypnea	1	22	0.000
Kussmaul's breathing	0	4	0.55
Dehydration	0	20	0.0001
Altered sensorium	0	19	0.0165
Shock at presentation	0	22	0.0000

DISCUSSION

The demographic characteristics of the patients presenting with DKA were studied. The findings from the present study suggest that DKA can present in children at an early age. It was found that the mean age of presentation of DKA in our study was 9.8 years. In the study done by Basavanthappa SP et al and Bhardwaj et al it was reported to be 7.52 years and 11.4 years.[5,6]

In our study , the incidence of DKA was high in early adolescent group (53%). In a study done in south India by Padma BK. et al study, the frequency of ketoacidosis was also more in the early adolescence group (48.1%).[7] Similarly in study by Vasudev K. et al, majority of patients (66%) were in the age group of 10–14 years.[8] But in a study done in Kuwait by Shaltout A. et al, the incidence of ketoacidosis was high in children less than 2 years of age.[9] It is inferred that in Indian population the incidence of DKA is more in early adolescent and adolescent age group.

Eighty percent patients admitted in this study were girls with a female to male ratio 4:1. In a study done in Kerala, the frequency of girls presenting with DKA was 57.7% DKA with female-to-male ratio (1.36:1).[7] However, contrary to our study, Syed M. et al study found a male preponderance as 66% patients were males.[10] The reason for more females being affected than males may be due to several reasons; the females from rural background and low socioeconomic strata are often neglected and medical attention is sought late when the disease progresses to a decompensated stage.[11]

Two patients (6%) had a history of 1st degree relatives having T1DM in the current study which was similar to findings in Prasad D et al. study where 5% patients had 1st degree relatives having T1DM.

Majority of the patients presented with severe DKA (73.3%) whereas 20% and 6.7% patients had mild and moderate DKA respectively. The reason for this observation could bethe low socioeconomic status or low parental education. Our centre also receives referrals from peripheral district hospitals where most often these patients are treated non specifically for the presenting symptoms.

This study also noted that amongst already diagnosed cases of T1DM, only 1 patient was on basal bolus regimen of short acting – regular insulin and long acting glargine insulin whereas all other patients were on conventional insulin therapy (mixtard insulin).

Of all the patients, 22 patients were admitted and managed in the PICU for severe DKA, whereas 8 patients were managed in the wards. In this study, all the patients with T1DM presented with DKA. Similarly, in the study by Prasad D. et al, majority (92.5%) of the patients of T1DM presented with features of DKA.[12] Unlike our findings, only 41.9% patients were admitted with DKA in Xin Y et al study.[13] Delayed diagnosis and early referral from primary care center may have led to development of DKA and hence the increased number of patients presenting with DKA. While 63.3 % of the patients were known cases of T1DM, 36.7% of the patients presented for the first time with DKA. In the study by Bhardwaj P. et al, 48.2% were newly diagnosed and 51.8% were previously diagnosed cases of diabetes.[6] There was no statistically significant difference in proportions of severity of DKA among known and new cases (p value – 0.8)

Data from our study shows that the most common precipitating factor for DKA in all patients was infections (72%). In previously diagnosed patients of T1DM, now presenting as DKA; infection was seen 57.8%, missed dose of insulin was found in 30% and inadequate insulin therapy was found in 40 % percent patients. In a study by Padma BK. et al, 50% had infection as the predisposing factor; omission of insulin was seen in 15% children.[7] In Basavanthappa SP et al. study, the cause for readmission was infection in (50%) and skipping of insulin in 30% cases.[5]

Musey et al reported the most common cause of DKA was stopping insulin therapy in the known diabetic patients, occurring in 67% of episodes.[14] It was also noted that in already diagnosed patients of T1DM, the patients had poor compliance of taking insulin which could have precipitated DKA. In these children, prompt medical support, knowledge about early sickness management would have prevented the recurrence of DKA. This highlights the importance of proper treatment of intercurrent illness, strengthening of follow up care of patients and parental education.

Most patients in our study had classical presenting features of T1DM like fever(73.3%), polyuria and polydipsia (73.3%), vomiting(63%) and fast breathing(63%). Two patients presented with cellulitis at the site of insulin injection (abdominal cellulitis and limb cellulitis). Since the symptoms of DKA are non-specific, it is found that often they are treated as either respiratory tract infections or misdiagnosed as pneumonia and gastroenteritis, leading to delay in diagnosis. It is yet more challenging to diagnose DKA in a newly diagnosed DM patient due to lack of awareness regarding signs and symptoms of T1DM among general population and primary care physician and this contributes to T1DM complicating as DKA.

The mean duration of illness before hospitalization was 7.7 days. In the study by Padma BK et al and Basavanthappa SP et al, the mean duration of symptoms was 10.10 days and 9.6 days.[5,7]Among the physical signs observed, tachypnea and shock at the time of admission was found in 76% patients whereas dehydration and altered sensorium was seen in 66% and 63% respectively. Kussmaul's breathing was present in 13% patients. In Padma BK. et al study, dehydration was present in 46.15% cases[7] , shock at presentation was seen in 19% patients, altered sensoriumand Kussmaul breathing was seen in 28.84%, and 13% patients respectively.

The mean pH at the time of admission and after 12 hours and 24 hours was 6.93±0.12,7.14±0.09 and 7.33±0.06 respectively. The mean pCO2, HCO3 was 12.39±3.16 and 6.16±2.09 respectively. The mean blood glucose of 15 patients which were recorded on glucometer was 420mg/dl and in the remaining 15 patients the glucose reading was recorded as HI. Comparable result by Prasad D. et al mentioned the mean Blood sugar as 459.22mg/dl.[12]Mean serum sodium level is 132.89 ± 6.623 and mean serum potassium level – 3.99 ± 1.95. 43% patients had hyponatremia at the time of presentation and 20% patients had hypokalemia. In a study by Kanwal SK. et al hypernatremia and hypokalemia were observed in 20%, and 14.5% respectively.[15]In the study by Vasudev K et al, 41.17% of cases had hypokalemia during acidotic phase.[8] The reason for presence of hypokalemia is attributed to the fact that potassium is usually lost as a result of vomiting, osmotic diuresis and secondary hyperaldosteronism due to volume depletion. In our study, hypokalemia improved after rehydration and electrolyte replacement. Only 2 patients required Stock solution for correction of persistence of hypokalemia.

Blood cultures were positive only for 4 patients. In study in Bhardwaj P et al study, blood cultures were reported to be positive in 13 % of the patients.[6] Both the patients who presented with cellulitis had staphylococcus aureus in their blood culture reports and these patients were successfully treated with antibiotics.

All the patients presenting with severe DKA in present study were managed according to the Milwalkuee regimen. Intravenous fluid, oxygen inhalation and insulin infusion was required in 22 (73%), 21 (70%) and 24 (80%) patients respectively. Out of all patients with severe DKA, only (13%) required more than 1 bolus and only 2 patients (6%) had to be started on ionotropic support as opposed to Prasad D. et al study in which 20% patients required ionotropic support.[12] Continuous insulin infusion was required in 24 patients(80%) who presented with DKA in the acute phase whereas 6 patients (20%) were managed directly with subcutaneous insulin. In Prasad D. et al study, insulin infusion was required in 87.5% patients.[12] The initial infusion of insulin was started at 0.1 IU/kg/hr. Two patients in the current study required escalation of insulin infusion rate (6.6%).

HCO3 therapy was not given to any patient in our study. Only 1 patient (3%) required mechanical ventilation. In the study by Bhardwaj P et al, 3 patients required mechanical ventilator support.[6] Shock was present in a total of 22 (73.3%) patients at the time of presentation. Cerebral edema was found in 4 patients (13.3%), all of which had been referred to our hospital after being managed in the peripheral hospitals and were found to have severe DKA. Kanwal et al reported cerebral edema

in 14.5%.[15] AKI was seen in 11 patients (33.3%), all of them recovered with prompt therapy, and were labeled as pre renal AKI.

The mean length of DKA resolution was 17.1 hours. The study in Shimla noted the mean length of DKA resolution as 16.8 hours.[6] The mean subcutaneous insulin requirement after control of DKA was 1.4IU/kg/day.

In our study only one patient (3.3%) died of cerebral edema and Pulmonary tuberculosis. Madiha Syed et al in their study reported 3.4% deaths in patients with DKA.[10] Our study found only 2 patients (6%) of T1DM had hypothyroidism and had to be started on thyroxine therapy.

Limitations

The study population was limited to 30 patients which is not representative of our entire population ,as many patients are lost due to late diagnosis and inadequate treatment before being referred to our tertiary care centre .

CONCLUSION

The present study describes the clinical profile, complications and outcome of diabetic ketoacidosis and associated co-morbidities in children admitted to the tertiary care public health institute of Madhya Pradesh. Majority of the patients admitted were females and majority of the patients admitted presented with severe DKA. Infection was the most common predisposing factor for DKA in the current study followd by missed insulin doses and inadequate doses. This poor compliance is an important modifiable precipitating factor for diabetic ketoacidosis in children in our population. Most common symptoms at admission were fever and osmotic symptoms like polyuria and polydipsia. Early recognition with high clinical suspicion and confirmed by appropriate laboratory screening helps in identifying children with diabetic ketoacidosis. Hypokalemia and hyponatremia were the main metabolic derangements associated with DKA in the current study. It is inferred that frequent clinical and laboratory monitoring is essential to recognize and address complications, like cerebral edema. Four patients in the current study had cerebral edema which were managed with anti-edema measures. For the long- term management strategy it is important to educate patients and their parents regarding regular blood sugar monitoring and insulin dosing. Much new-onset DKA can be prevented by increased awareness of early signs and symptoms of diabetes. Routine follow up to the hospital will help titrate insulin and early recognition of complications ofT1DM. This will lead to overall improvement of outcome of patients. More efforts should be put into preventing the occurrence of DKA at initial presentation.

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