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Original Research Article

The Study of Independent Mortality Indicators in Patients of Diabetic Ketoacidosis

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Abstract

Background: Diabetic ketoacidosis (DKA) is an acute complication of uncontrolled diabetes mellitus that is associated with increased morbidity and mortality.

Objective: To identify independent mortality indicators in patients of DKA so as to stratify them according to risk for emergent intensive care.

Material and Method: The study sample consisted of 110 patients diagnosed of DKA admitted to SMS hospital. All the patients were treated according to standard protocol. Detailed history, type of diabetes, presence of coexisting diseases, level of consciousness, vitals, capillary blood glucose, units of regular insulin administered to decrease blood glucose to less than 250 mg/dl , liters of normal saline administered and urine output were monitored. WBC count, blood urea, serum creatinine, serum electrolytes, arterial blood pH and bicarbonate, liver function tests, HbA1c, ECG and chest X ray were done. The above parameters and relevant investigations were monitored till the patient was cured and discharged or lost to death. The data was analyzed.

Results: Ketonuria more than 3+, glucosuria more than 4+, presence of circulatory shock, fever and/or depressed mental status in the first 24 hours, requirement of more than 6 liters of fluids in first 24 hours; pH <7.1 and HCO3 < 11meq/l at presentation, time taken to become ketone free more than 96 hours or less than 48 hours had significant association with higher rates of mortality, while patients who were normotensive or hypertensive at presentation and those who took 48-95 hours to become ketone free had significantly lower rates of mortality. Age, sex, whether diagnosed newly or established case of diabetes, type of diabetes, presence of comorbidity, number of units of insulin required to bring the blood sugar levels to less than 250mg/dl in the first 24 hours, level of blood sugar at the time of presentation did not have a significant association with mortality.

Conclusion: Mortality was higher among those who had ketonuria >3+, glucosuria >4+, lower respiratory tract infections, presence of circulatory shock, depressed mental status, fever in the first 24 hours, pH <7.1, HCO3-<11 meq/l at presentation, duration taken to become ketone free either too early (24-48 hours) or too late (>96 hours), requirement of >6L fluid on admission. Hence the high mortality rate in this study (38.18%) was due to multi-factorial reasons. It could have been confounded by the fact that the study was conducted during the ongoing covid pandemic. Risk stratification of patients with DKA is possible from

simple clinical and laboratory variables available during the first day of hospitalization and prompt recognition of the above risk factors either at admission or during the course of management in the ward has to be followed by emergent ICU care to reduce the mortality.
Keywords: Diabetic ketoacidosis, mortality indicators

Introduction

Diabetic ketoacidosis (DKA) is an acute complication of uncontrolled diabetes mellitus that is associated with increased morbidity and mortality. It more commonly occurs in patients with type 1 diabetes, though it can also occur in patients with type 2 diabetes. In both populations, catabolic stress of acute illness or injuries such as trauma, surgery, or infections may be a trigger. Common precipitating factors for DKA are non-compliance, new-onset diabetes, and other acute medical illnesses. The most common types of infections that can precipitate DKA are pneumonia and urinary tract infections.

DKA is characterized by hyperglycemia, metabolic acidosis, and increased circulating total body ketone concentration. Ketoacidosis results from the lack of or ineffectiveness of insulin with concomitant elevation of counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) [1,2]. This leads to altered glucose production and disposal and increased lipolysis and production of ketone bodies. Hyperglycemia results from increased hepatic and renal glucose production (gluconeogenesis and glycogenolysis) and impaired glucose utilization in peripheral tissues.[1] In addition, both hyperglycemia and high ketone levels cause osmotic diuresis that leads to hypovolemia and decreased glomerular filtration rate. The latter further aggravates hyperglycemia [3]. Fluid resuscitation and maintenance, insulin therapy, electrolyte replacement, and supportive care are the mainstay of management in diabetic ketoacidosis.

Materials and Methods

Patients diagnosed to have DKA admitted to SMS hospital during the study period and fulfilling the inclusion and exclusion criteria were included in the study. All the patients were treated according to standard protocol. Detailed history-presenting symptoms, precipitating factors, age, presence or absence of fever, depressed mental status were noted. Type of diabetes, presence of coexisting diseases like hypertension were noted. Presence of depressed mental status-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 to decrease blood glucose to less than 250 mg/dl, liters of normal saline administered and urine output were monitored. Routine investigations: WBC count, renal function tests, serum electrolytes, arterial blood pH and bicarbonate, liver function tests, HbA1c, ECG and chest X ray were done. The above parameters and relevant investigations were monitored till the patient was cured and discharged or lost to death.

The data was analyzed.

Inclusion criteria: All patients having known, or unknown diabetes hospitalized

at SMS medical college, Jaipur with a diagnosis of DKA - blood glucose >250mg/dl, arterial pH <7.35, bicarbonate <15 meq/l and ketonuria, age =/ >15 years and patients who had given informed consent to participate in the study.

Exclusion criteria- Pregnant women, patients with preexisting chronic illnesses like coronary artery disease, congestive cardiac failure, anemia, liver and renal impairment, those not treated according to standard protocol, age <15 years and patients who had given negative consent to participate in the study.

Results

Presentation in the age group 36-45 years had the best rates of survival- 70.3%, while age more than 65 years had higher rates of mortality -68.75%. Females had a higher fatality rate of 42.1% compared to males 36.1%. Mortality rate among type1 DM patients was 35.29%, while it was slightly higher among type 2 DM patients- 40.86%. 80% cases were known cases of diabetes and 20% cases were newly diagnosed diabetes mellitus presenting as DKA, of which 36.36% died while, 38.63% of known cases of diabetes died. Those who were normotensive at presentation had a better survival rate of 87.3%, so did patients with a systolic blood pressure more than 140 mm Hg (75%) as compared to those with hypo-tension.

Patients with urine ketone less than 3+ at presentation had a lower mortality rate of 16.3%, compared to equal to or more than 3+ at presentation (55.7%). Patients with urine glucose 2+ and 3+ fared better in terms of mortality (20.68% and 14.28% respectively) compared to those presenting with urine glucose 4+ (87.17%). 47.36% was the mortality rate among the patients with a co morbidity as opposed to 33.33% among patients without any co-morbidity.

Patients with bacterial or viral pneumonia with DKA had a mortality rate of 63.88% while urinary infections and other infections caused 28% mortality, the group with the least mortality was drug defaulters- 16.12%. 60.34% of patients presenting with depressed mental status in first 24 hours died, 48.33% of those presenting with fever in first 24 hours died and an overwhelming 90.62% of the patients presenting with circulatory shock in the first 24 hours could not be saved. Highest rates of mortality was witnessed in the group requiring >110 U insulin in first 24 hours to reduce the RBS to <250mg/dl - 47.36%, followed by those requiring 91-110 U- 40.62%, the least mortality was in the group requiring less than or equal to 50U- 8.33%. In 73.64% cases, fluid requirement was >6 L in 24 Hours. Among them, 45.67% died, compared to 17.24% mortality among patients who required less than 6-liter fluid in the first 24 hours. Patients presenting with a pH <7.1 had a higher mortality rate of 46.67%, compared to those presenting with a pH >7.1 (19.35%). Patients with a bicarbonate level less than or equal to 11 meq/l had a higher mortality rate of 51.16% compared to those presenting with a bicarbonate level more than 11 meq/l (29.85%). 30% of patients who took more than 96 hours to become ketone free had died, compared to 25% who took 24-48 hours to wash ketones and died, 10.63% who took 49-96 hours to wash off ketones and died, considering that 22.72% of the sample size died without becoming ketone free. Among the patients who presented with an RBS >500mg/dl, 36% died, compared to 40% mortality among those who presented with an RBS <500mg/dl.

Table 1: Relationship between presence of comorbidities and mortality

Presence of comorbidities	Alive		Dead		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
No	48	66.67	24	33.33	72	65.45
Yes	20	52.63	18	47.37	38	34.55

Chi square statistic is 2.0758. P value is 0.1496

Table 2: Relationship between precipitating factors and mortality

Precipitating factor	Alive		Dead		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Drug defaulter	26	83.87	5	16.13	31	28.18
Viral pneumonia	13	52	23	92	25	22.73
Bacterial pneumonia					11	10
Urinary tract infections	7	70	3	30	10	9.09
Acute Gastroenteritis	2	100	0	0	2	1.82
Cellulitis/ Diabetic Foot	1	50	1	50	2	1.82
Chikungunya fever	1	50	1	50	2	1.82
Dengue fever	1	50	1	50	2	1.82
Pulmonary tuberculosis	2	100	0	0	2	1.82
Bacterial meningitis	1	100	0	0	1	0.91
Mucormycosis	2	100	0	0	2	1.82
Pyonephrosis	0	0	1	100	1	0.91
Tubercular Pleural Effusion	1	100	0	0	1	0.91

Table 3: Relationship between clinical status in first 24 hours and mortality

Clinical status in first 24 hours	Alive		Dead		Total	
Depressed mental status	23	39.66	35	60.34	58	52.72
Fever	31	51.67	29	48.33	60	54.55
Circulatory shock	3	9.38	29	90.63	32	29.09

The Chi square statistic is 17.9868. P value is 0.0001

Table 4: Relationship between time taken to become ketone free and mortality

Time taken to become ketone free	Alive		Dead		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Not ketone free	0	0	25	100	25	22.73
24-48 hours	6	75	2	25	8	7.27
49-96 hours	40	85.11	7	14.89	47	42.73
More than 96 hours	21	70	9	30	30	27.27

The Chi square statistic is 47.6467. P value is <0.00001

Table 5: Relationship between pH and bicarbonate levels at presentation and mortality

At presentation	Alive Number	Alive Percentage	Dead Number	Dead Percentage	Total Number	Total Percentage
pH <7.1	40	53.33	35	46.67	75	68.18
pH <7.1	28	80.00	7	20.00	35	31.82

chi-square statistic is 7.1895. The p-value is 0.0073						
HCO3 <11	21	48.84	22	51.16	43	39.09
HCO3 <11	47	70.15	20	29.85	67	60.91
chi-square statistic is 5.04. The p-value is .0247						

Discussion

Age of presentation, sex, type of diabetes, whether the patients were newly diagnosed or established cases of diabetes, the number of units of insulin required to bring the blood sugar levels to less than 250mg/dl in the first 24 hours or the level of blood sugar at the time of presentation - did not have a statistically significant effect on mortality.

There was no statistical difference in mortality among those who had comorbidity and those who didn't. The most common comorbidity noted in this study was hypertension-86%. Presence of comorbidities especially when uncontrolled leads to micro and macro vascular end organ damage, that in turn makes the management difficult- like nephropathy or coronary artery disease- in these conditions fluid replacement needs to be very judicious and under constant, strict monitoring. However, in our study, the difference was statistically not significant.

There was statistically significant difference in mortality rates among those who were normotensive or hypertensive on presentation compared to those who were hypotensive on presentation, with those who were hypotensive having higher rates of mortality. Maintenance of intravascular volume in the context of ongoing hyperglycemia and glycosuria is a difficult task. Hence, at presentation when the patient was normotensive or slightly hypertensive, it proved to be beneficial in the management, in our study.

There were higher rates of mortality among : those who had ketonuria more than 3+ and glucosuria more than 4+ at presentation, those who presented with circulatory shock (relating to the fact that oliguria sets in and multi organ dysfunction occurs due to hypo perfusion secondary to shock, rates of survival become less) and those who presented with depressed mental status in the first 24 hours probably relating to the cerebral edema secondary to rapid metabolic disturbances and consequent corrections

There was significant increase in mortality among the group who required more than 6 liters of fluids in first 24 hours and those presenting with pH <7.1 and HCO3 < 11meq/l. Sree Kumar et al [5] reported patients with pH value less than 7.15 had increased risk of mortality and 6 patients had bicarbonate level less than 10mEq/L and was associated with 50% increased risk of mortality. Warsha Ahuja et al [8] found in their study that depressed mental status, low p^H, low bicarbonate levels, high potassium levels, RBS >300mg/dl, >6 litres of fluid requirement in the first 24 hours, >50 IU of insulin requirement in first 12 hours, Urine ketone positive for >12 hours, fever in the first 24 hours were indicators of mortality.

There was increased mortality among patients who took more than 96 hours or less than 48 hours to become ketone free. Patients who took 49-95 hours to wash ketones had better rates of survival. Hence neither a rapid washout nor a delayed washout of ketones was observed to be beneficial in our study, rather a moderate slow and steady washout between 48-96 hours after presentation proved to be most beneficial for survival.

The group of drug defaulters had the lowest mortality rates-16.12%, compared to patients with pneumonias-63.8% followed by urinary infections and other infections-28%. This can be explained by the fact that when a patient has defaulted the drug and does not have any other

precipitating factor or complication, supportive care and acute management of DKA yields the best results, whereas when another superimposed condition poses complications, it becomes difficult to manage, as was observed in the cases of pneumonia-bacterial and viral (covid and non-covid) where the mortality cannot be attributed in absolute terms to either the pneumonia itself or to DKA. Both factors are probably synergistic in causing death. In a study by MG Mahesh et al [9] they failed to identify an independent mortality factor, but adverse parameters more than 5 was significantly associated with death. [10]

In our study out of total 110 cases 61.82% were alive and 38.18% cases had died. Elmehdawi and Elmagerhei[4] found 10% death in their study. Wu et al [6] found 10.8% mortality in their study.

Sree Kumar et al [5] reported that overall mortality was 13.6%. Zaynab Aloufi et al found the in-hospital mortality rate in DKA to be 11.3%. [7]

Conclusion

Risk stratification of patients with DKA is possible from simple clinical and laboratory variables available during the first day of hospitalization and prompt recognition of the above risk factors either at admission or during the course of management in the ward has to be followed by emergent ICU care to reduce the mortality. However, the high mortality rate in this study (38.18%) was due to multi-factorial reasons. Some may have been due to therapy-related factors such as errors in management. Further studies are needed to clarify the factors behind this high mortality rate and steps to reduce the rate should be taken. The small sample size of this study, and the fact that it was a hospital-based prospective study conducted at a teaching hospital given that most of the patients had been referred from the periphery more than 24 hours after presentation, the clinical parameters and treatment given could not be ascertained to a definite extent. The sample size included mostly hypertension as a comorbidity, those with coronary artery disease or chronic kidney disease had been excluded in the beginning of the study to avoid confounding in mortality. However, as these conditions coexisting with DKA could be a strong predictor of mortality, comorbidity as a whole cannot be dismissed as an indicator of mortality based on this study. Most of the sample size that had lower respiratory tract infections has been assessed during the ongoing covid pandemic, with pneumonia accounting for 54.76% of mortality rates, hence mortality rates could not be attributed in particular to any condition in the presence of an evolving and nascent disease like covid pneumonia.

Work attributed to:

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