Risk factors for mortality in children with diabetic keto acidosis from developing countries

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Abstract

Diabetic keto acidosis (DKA) is the major cause for mortality in children with Diabetes mellitus (DM). With increasing incidence of type 1 DM worldwide, there is an absolute increase of DM among children between 0-14 year age group and overall incidence among less than 30 years remain the same. This shift towards younger age group is more of concern especially in developing countries where mortality in DKA is alarmingly high. Prior to the era of insulin, DKA was associated with 100% mortality and subsequently mortality rates have come down and is now, 0.15%-0.31% in developed countries. However the scenario in developing countries like India, Pakistan, and Bangladesh are very different and mortality is still high in children with DKA. Prospective studies on DKA in children are lacking in developing countries. Literature on DKA related mortality are based on retrospective studies and are very recent from countries like India, Pakistan and Bangladesh. There exists an urgent need to understand the differences between developed and developing countries with respect to mortality rates and factors associated with increased mortality in children with DKA. Higher mortality rates, increased incidence of cerebral edema, sepsis, shock and renal failure have been identified among DKA in children from developing countries.

Root cause for all these complications and increased mortality in DKA could be delayed diagnosis in children from developing countries. This necessitates creating awareness among parents, public and physicians by health education to identify symptoms of DM/DKA in children, in order to decrease mortality in DKA. Based on past experience in Parma, Italy it is possible to prevent occurrence of DKA both in new onset DM and in children with established DM, by simple interventions to increase awareness among public and physicians.

Key words: Diabetic keto acidosis; Mortality; Cerebral edema; Sepsis; Shock; Delayed diagnosis

Core tip: Mortality in Diabetic keto acidosis (DKA) among children from developed countries is due to cerebral edema and is very low. The mortality in DKA among children from developing countries is due to higher incidence of cerebral edema, sepsis, shock and renal failure. Delayed diagnosis is the root cause for high mortality in children with DKA from developed countries. There is an urgent need to increase the awareness about diabetes among the public and physicians.

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INTRODUCTION

Diabetes mellitus in children is on the rise for past few decades. On an average 78000 children are diagnosed with diabetes every year[1]. One among every five children with newly diagnosed type 1 diabetes mellitus (DM) is

found to be an Indian[1]. In this world pandemic of diabetes with efforts to control type 2 DM it is easy that the needs of type 1 DM who are only 10% of people with diabetes is forgotten. Occurrence of type 1 DM is on the rise among children between 0 and 14 years of age. Majority of children present with diabetic keto acidosis (DKA) at onset and this rate is inversely proportional to prevalence of DM in the population[2]. Death in DM is predominantly due to DKA. Mortality rates in developed countries and developing countries show much variation. Similarly the cause for mortality in DKA varies between developed countries and developing countries. Cerebral edema is the predominant cause for mortality in children with DKA from developed countries, while recent data from developing countries has shown higher incidence of cerebral edema, sepsis, shock and renal failure as the cause for death in DKA[3]. Delayed diagnosis has been identified as a major risk factor associated with mortality in children from Chennai-India[3].

Overall mortality in children with DKA varies from 0.15% to 0.35% in developed countries like Canada, United States and United Kingdom[4-7] and from 3.4% to 13.4% in developing countries like India, Pakistan and Bangladesh[8-14]. Cerebral edema is the major cause for mortality in DKA[15,16]. Occurrence of cerebral edema varies from 0% to 5.5% in developed countries[17-19] and is reported to vary from 24%-26% in developing countries[10]. Literature on reasons for such high mortality and associated factors for death in children with DKA in developing countries are very recent and majority of these are based on retrospective studies. Whether factors associated with mortality are pre hospital in nature or treatment related needs to be understood. In the editorial published in Indian Pediatrics during the year 2004, titled "What determines the outcome of DKA in children from a developing country?" author has raised issues regarding fluid therapy in DKA[20]. The role of amount and rate of fluid administration in the management of DKA associated cerebral edema is still controversial. Traditionally cerebral edema has been linked to fluid therapy in DKA. A recent article titled 'Warning from India' has addressed the issue of high mortality and high incidence of sepsis and cerebral edema in children with DKA from a developing country[21]. Association of sepsis may have a great impact on fluid therapy in DKA.

DKA RELATED CEREBRAL EDEMA

Cerebral edema has been the major risk factor for mortality in children with DKA world over. Despite decades of management of DKA the exact cause for cerebral edema in DKA is yet to be understood. Whether hypo perfusion related ischemia leading to cytotoxic edema or reperfusion induced vasogenic edema, is the cause for cerebral edema is controversial. However initial cytotoxic edema followed by subsequent vasogenic edema can very well contribute to development of cerebral edema in DKA. Also the role of inflammatory mediator release, glucotox-

icity, uremia or acidosis in causing cerebral edema, is not clearly understood. Occurrence of cerebral edema can be at the time of presentation or during therapy up to initial 24 h. Predisposing factors for cerebral edema in children with DKA have been identified in various studies in developed countries. Identified factors are disease related or treatment related or both. Identified factors vary from young age at presentation, new onset disease, rate and amount of fluids used for resuscitation, blood urea nitrogen, body mass index, initial osmolality, rapid fall in osmolality, failure of sodium to rise with treatment, use of bicarbonate for correction of acidosis, insulin infusion in the first hour of therapy of DKA or bolus insulin therapy in DKA[22-30]. There has been no consistency among the factors identified for occurrence of cerebral edema in various studies published till date.

Occurrence of cerebral edema from developing countries has been found to be as high as 26% among a cohort of children admitted at a pediatric intensive care unit in north India[11]. Literature on reasons for such high incidence of cerebral edema from developing countries is very scarce. Studies by Tiwari et al[11] from Chandigarh-India have identified fluid refractory shock, higher volume of fluids at admission and respiratory failure requiring ventilation to be significant risk factors for cerebral edema in DKA. However only fluid refractory shock, azotemia and younger age were identified to be significant risk factors for cerebral edema in multivariate analysis[11]. Literature from Chennai-India has revealed cerebral edema in 24% of study group[3]. In this prospective study of 118 children with DKA, specific risk factor related mortality for cerebral edema was 43%. A higher fluid bolus at the emergency room for resuscitation was a significant therapy related factor for cerebral edema by univariate analysis. Cerebral edema was significantly associated with altered sensorium, lower $PaCO_2$ at admission, delayed diagnosis and failure of sodium to rise with therapy by multivariate analysis. Both the studies from India have identified higher fluids as risk factors for cerebral edema in univariate analysis but were not significant in multivariate analysis[3,11]. This may be an important observation in developing countries where sepsis has been an important factor associated with increased mortality in children with DKA. Too much of fluid for resuscitation resulting in cerebral edema is still controversial in DKA. Similarly less fluid in a child with DKA and shock may also worsen risk of cerebral edema and renal failure. Sepsis by itself will demand large volumes of fluid boluses in a child. Hence recommendations regarding fluid therapy based on guidelines from developed countries where sepsis and shock are not major factors in children with DKA needs to be addressed for future guidelines when applied to developing countries. Whether there is a need for more liberal fluid therapy in DKA in developing countries where sepsis, shock and renal failure have been identified to be risk factors for mortality needs to be addressed by multicentric trials.

SEPSIS IN DKA

Sepsis in DKA as a risk factor for increased mortality has been identified in studies form developing countries like India, Pakistan and Bangladesh[8-12,14]. Majority of these studies were based on retrospective data. Still they have identified sepsis as a definite risk factor for mortality in children with DKA. Though infections have not been identified to be a major comorbid state in children with type 1 diabetes from developed countries, studies from Chennai-India has shown that infections are much more common in children with diabetes in comparison to children without diabetes[31]. In this context infections do play a major role in children with DKA. Sepsis not only precipitates DKA, also complicates fluid therapy, predisposes to renal failure and is associated with increased mortality in DKA based on data from developing countries. Jayashree et al[10] in 2004 from India published their retrospective study in DKA. They reported that among 64 children with DKA 30 children had foci of infection. Respiratory infection in 10, soft tissue infection in 10, meningitis in 3, hepatitis in 2, peritonitis, chronic suppurative otitis media, tonsillitis, ethmoiditis and oral and vulval candidiasis in one each. Cerebral edema and complicating sepsis were reported to result in poor outcome in children with DKA. In their series, sepsis was the triggering factor in one third of cases. In study from Chennai-India, infections were encountered in 61 children among the study group of 118 children[3]. Of these 49 had identified focus of infection (41.5%). Culture positive sepsis was seen in 12% of children with DKA and is associated with specific risk related mortality of 57%. Other infections encountered were pneumonia, urinary tract infections, skin and soft tissue infections, mucormycosis, acute suppurative otitis media, enteric fever and peritonitis. Kanwal et al[12] from Delhi India has identified 32.7% of study group (18 of the 55 children) to have sepsis. Documented infection were reported to be 16.3%. Urinary tract infection, pneumonia, diaorrhea and culture positive sepsis were the identified infections. Study by Tiwari et al[11] published in 2012 had revealed 58% of study population as sepsis as per standard definition. However only 1/5th of this group had a focus of infection identified. Respiratory tract was the focus in 6, gastrointestinal in 4, sinonasal mucormycosis, urinary tract infection (UTI), acute otitis media, peritonitis, tonsillitis and cellulitis one each. Infections have been reported in 48% of children with DKA by Zabeen et al[14] from Bangladesh. Mortality in their study group were attributed to cerebral edema and sepsis. Respiratory infections were commonest followed by urinary tract infections, sepsis and pneumonia.

Studies from Iran by Asl et al[32] reported that among 63 children with DKA 13 of them had infections. This was inclusive of pneumonia, tuberculosis, diarrhea and upper respiratory infections. The study documented acute renal failure in 4.7%. Clinical diagnosis of sepsis as well as shock may be over diagnosed in children with DKA. Presence of fever in DKA signifies infection and the focus need to be identified. The criteria for systemic inflammatory response (SIRS), when applied to children with DKA may lead to over diagnosis of sepsis. Tachycardia and tachypnea as criteria can be explained by dehydration and keto acidosis rather than sepsis and lactic acidosis. Lactic acidosis in DKA could be due to sepsis, hypovolemia or due to disturbed carbohydrate metabolism perse. Similarly DKA is known to be associated with leucocytosis and this is not specific for sepsis in DKA[33]. Leukocytosis is a part of stress response in DKA and may be seen in up to 50%-60% of children with DKA[34]. One needs to be very cautious about diagnosing sepsis based on the criteria for SIRS in DKA. Any child with fever or a focus of infection along with any of the above criteria can be taken as sepsis complicating DKA. Current guidelines from developed countries where sepsis is not a major factor, do not recommend antibiotics in DKA. Based on literature evidence from developing countries, sepsis is more common and sepsis complicating DKA has increased mortality. Hence antibiotics may be empirically considered in children with fever or refractory shock despite the absence of obvious focus of sepsis, until infections have been ruled out in DKA among children from developing countries.

SHOCK IN DKA

Shock as a presentation in DKA is rare in literature from developing countries[35]. International Society for Pediatric and Adolescent Diabetes clinical practice consensus guidelines 2009 compendium states the following "Despite of their dehydration, patients continue to maintain normal blood pressure and have considerable urine output until extreme volume depletion and shock occurs, leading to a critical decrease in renal blood flow and glomerular filtration"[36]. However it is uniformly reported in literature from developing countries that shock at presentation in children with DKA is fairly common. Studies from Pakistan[8] have revealed incidence of shock to be 19.3% in their study and overall mortality was 3.4%. Tiwari et al[11] from Chandigarh, India documented in their study that 48% of study population with DKA at the pediatric intensive care unit had hypotensive shock at presentation and of them 30% needed inotropes. Kanwal et al[12] from India have documented in their study on 55 DKA children, incidence of shock to be 18.1%, 10.9% were due to hypovolemia and 7.25% were due to septic shock. Study from Chennai[3] has shown occurrence of shock at presentation in DKA to be 12% and specific risk factor related mortality in DKA to be 53%. According to another study from Chennai, India among the 23 children with DKA 10 presented with shock[37]. However criteria used to assess shock in those children and severity of shock had not been discussed. Shock in DKA is a combination of hypovolemia and sepsis. To differentiate between the two is difficult and most of the time it may be a combination of hypovolemia and sepsis. The clinical evidence for hypovolemia in DKA is not reliable

as published in literature. Intra cellular dehydration in DKA may not be clinically evident and hence degree of dehydration may be under diagnosed. Capillary refill time in DKA cannot be relied as a sign of shock in DKA[38]. Tachycardia could be a physiological response to dehydration in DKA and this needs caution while interpreting it as a sign of shock. Tachypnea for similar reasons is due to acidosis which is predominantly keto acids and cannot be interpreted as a sole evidence of hypo perfusion and lactic acidosis. Altered sensorium in DKA can be explained by cerebral edema, severe acidosis or shock in DKA. This feature cannot be relied as a sign of poor end organ perfusion of shock. In developing countries where cerebral edema, shock, sepsis and renal failure are reported to be common in DKA, diagnosis based on clinical features alone may be challenging for the pediatrician at the emergency department. Hence the criteria for septic shock or hypovolemic shock may need to be applied with clinical judgment in children with DKA. Presence of fever, hypotension, wide pulse pressure in septic shock, clinical evidence of dehydration in hypovolemia may be better indicators of type of shock in DKA. Similarly is the assessment of dehydration in shock. Clinical signs of dehydration may not be evident in DKA. Since initial dehydration is predominantly intra cellular there may not be obvious clinical evidence of dehydration at presentation in a child with DKA. This might lead to underestimation of degree of dehydration in DKA. With recent literature from developing countries regarding shock and sepsis in DKA, we need to reappraise the existing guidelines from developed countries for fluid therapy in children with DKA. Whether less fluid is harmful or more fluid is harmful needs to be answered by well planned fluid trials for children with DKA from developing countries.

RENAL FAILURE IN DKA

Renal failure in children with DKA is a complication unheard of in literature from developed countries[39]. Children from developing countries presenting with renal failure in DKA is not uncommon. Studies from Iran by Asl *et al*[32] reports that 4.7% of children with DKA had acute renal failure. Studies from Bangladesh by Zabeen *et al*[14] have shown the incidence of renal failure to be 3.7% in DKA. Published literature from Chennai, India[40] revealed acute renal failure in DKA to be 11.5%. Mortality among children with DKA and acute renal failure was documented to be 40%-72%. Sepsis, shock and rhabdomyolysis causing acute renal failure have been reported in the series. Renal failure leads to difficulty in diagnosis as well as management of DKA. Oliguria and anuria as criteria for renal failure is not reliable in DKA due to osmotic diuresis of hyperglycemia. Similarly, urea and creatinine values may be elevated in DKA due to prerenal causes like dehydration which declines with adequate fluids. Subsequent elevation in creatinine cannot be taken as a definite criterion for renal failure as the commonly used calorimetric method of creatinine

estimation is likely to be associated with spurious elevation due to interference by ketones. Fluid restriction in a child with sepsis and shock (hypovolemic or septic) for fear of cerebral edema during management of DKA may predispose to renal failure. Child with severe dehydration with delay in diagnosis may present with acute tubular necrosis leading to renal failure in DKA. Management of renal failure in DKA poses great difficulty for the treating physicians. Following needs to be considered in renal failure in DKA-modification of amount and type of fluids for therapy, consideration of using bicarbonate, varied metabolism and sensitivity of insulin. Peritoneal dialysis in such children also leads to severe fluctuations of blood glucose levels. Presently there are no standard guidelines for management of renal failure in DKA among children. There is an urgent need for such guidelines based on the existing evidence from developing countries.

DELAYED DIAGNOSIS OF DKA

What predisposes children with DKA to such complications in developing countries needs to be addressed urgently. Delayed diagnosis in DKA has been identified to be one of the factors for mortality in DKA in studies from Chennai-India[3] and also recently has been presented as an e poster at a conference, from Chandigarh-India[41]. Children with diabetes presenting with DKA at the onset has been attributed to delay in diagnosis in developed countries. Missed diagnosis of DKA predisposing the child to DKA is common in literature. However delay in diagnosis as a significant risk factor for mortality in DKA has been identified only from India[3]. This study reported that children with DKA had 1-5 physician visits prior to diagnosis of DKA. Children with DKA were more likely to have consulted a physician prior to diagnosis of DKA as reported in literature from developed countries. Rosenbloom[39] from US had mentioned that children with new onset DKA has been seen in physician's office prior to diagnosis without adequate history and laboratory evaluation. In infants and young children symptoms may be nonspecific and this needs a high index of suspicion to diagnose DKA. Literature reports that DKA has been misdiagnosed as surgical emergencies with acute abdomen[42]. Bui *et al*[43] from Canada published that among 285 children with DKA, 38.8% and 1104 children with diabetes with no DKA, 34.4% had at least one medical visit during the week before diagnosis (*p*-026). Ali *et al*[44] had published in 2011 that 30% of newly diagnosed children have had at least one related medical visit prior to diagnosis, suggesting the condition is being missed by doctors. Majaliwa *et al*[45] from Africa mention in their article that DKA can easily be misdiagnosed as cerebral malaria or meningitis in busy emergency reception areas of most hospitals in Africa. Literature reveals similar studies from Tunisia and Tanzania[46,47]. However none of these studies have identified delayed diagnosis as a risk factor for mortality in children with DKA. Study from Chen-

Table 1 Reasons for delayed diagnosis in diabetic keto acidosis
Reason
Lack of parental awareness about diabetic symptoms
Lack of awareness among physicians
Mis-interpretation of diabetic symptoms
Exclusive treatment of intercurrent illness only
Lack of finger prick estimation of blood glucose
Non recognition of lab abnormalities
Lack of immediate referral
Delay in transport to appropriate center
Improper referral
Due to parental causes (native treatment, social reasons and economic constraints)

nai[3] has identified delayed diagnosis in DKA in 64.8% of children with new onset DKA. Eighty-four point seven percent of infants and 58% of school children with DKA had delayed diagnosis. Delayed diagnosis was encountered in 12 of 13 children who died of DKA in their study. Specific risk factor related mortality for delayed diagnosis was 21% in the study[3]. Factors identified for the delayed diagnosis in their study is summarized in Table 1. Tachypnea in DKA has been universally misdiagnosed as bronchopneumonia, bronchiolitis or acute severe asthma in children. Polyuria and polydipsia have been misinterpreted as UTI in most of the children. Abdominal pain is misinterpreted as worm infestation and acute gastritis. Dehydration in the presence of vomiting is usually treated as acute gastroenteritis. Recent onset bed wetting is seen as a sign of stress in school children. Literature reveals up to 15%-86% of children with DKA not been diagnosed as diabetic at the first physician consultation[43,44,48,49].

Delay due to missed diagnosis is universal in DKA among children from developed and developing countries. Literature also reveals that, simple estimation of blood glucose by capillary method using finger prick has been used very rarely in physician consultation room[3]. A simple investigation in the physician's consultation room could have led to the diagnosis in children who had their diagnosis missed prior to DKA. Similarly, laboratories did not alert the treating physician or the parent when they measured high blood glucose or documented glycosuria in children[3]. Inappropriate referral was again reason for delay in specific management as the facilities for management of DKA by a structured diabetic care team or intensive care pediatrician is not universally available in developing countries. All treating physicians should have access to the standard treatment protocols for management of children with DKA or should have an access to help through hot line facilities at times of need. These factors coupled with lack of knowledge about emergency free public transport facilities, economic constraints and unhealthy cultural practices lead to delay in management of DKA in children from developing countries.

CONCLUSION

Analyzing the magnitude of problems in DKA in chil-

dren from developing countries it is obviously evident that the mortality rates and reasons for such high mortality in DKA to be very different from developed countries. However majority of standard treatment protocols followed in developing countries are based on recommendation from developed countries. Root cause for majority of these complications could be delayed diagnosis of DKA. There is an urgent need for modified protocols for children with DKA and shock or renal failure. Fluid trials in such children is an urgent need of the hour. There exists difficulty in recognizing the symptoms of diabetes among parents and physicians[50]. With regard to delay in diagnosis there is a need for creating awareness among parents and physicians regarding clinical features of DM and DKA. The best strategy would be to identify DKA early and refer them to appropriate centers for management immediately. The laboratories should raise high risk alert immediately to the parent or the physician when they encounter a child's report with hyperglycemia and/or glycosuria.

As majority of the risk factors identified for mortality in DKA among children from developing countries are pretreatment factors, the ultimate aim of future programmes should be to prevent DKA in children. DKA occurring in new onset DM or in a known diabetic child is considered as a preventable health care failure. Vanelli et al[51,52] in Parma, Italy have proved that simple awareness programmes in schools and physicians office in the form of posters depicting signs of diabetes have helped over 5 years to reduce occurrence of DKA to zero. This has been proved to be successful even years after the programme was stopped. Studies from Australia have shown reduction in the rate of DKA at initial diagnosis of diabetes, during awareness campaigns[53]. Similar models with modification to local needs can help prevent delay in diagnosis of DKA among children from developing countries. Initiatives and awareness programmes need to be implemented in countries like India where the magnitude of the problem is likely to increase over years. It is time that emergency interventions are undertaken to minimize deaths in DKA in developing countries. Increased awareness among parents, school teachers and physicians is urgently warranted for early diagnosis and prevention of mortality in DKA. Creating awareness through nationwide diabetic awareness day can help an earlier diagnosis of DKA among children.

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