Review Article

Update Regarding Diabetic Ketoacidosis in Children and Controversies in Management

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ABSTRACT

Diabetic ketoacidosis (DKA) is a serious complication among pediatric population suffering from Diabetes Mellitus and it is associated with significant risk of life threatening complications resulting in increased morbidity and mortality. Overall the DKA management is well harmonized through recommended guidelines with a few emerging concerns relevant to the management and location of admissions for patients with different levels of severity of DKA, i.e., mild, moderate, severe. With emerging suggestions of revising the guidelines it is important to maintain the quality of care by careful evaluation of existing literature and properly designed future researches in pediatric population. Then to define the correct population of pediatric DKA patients who might be benefitted from the proposed revisions. Additionally, continuing awareness of primary health care providers is crucially important about the latest concepts as this can remarkably improve care in children having DM and DKA. Here is presented some literature review relevant to the emerging concerns with the aim to help improve quality of care. The aim of this article is to identify the controversies in management of DKA regarding managing patients in wards instead of PICU and intermittent insulin instead of insulin infusion, then to discuss the relevant basic patho-physiology, then it shall review the literature and lastly, to make suggestions regarding selection criteria of categories of patients who should be considered for non-insulin infusion therapy. These patients categories should be evaluated in future studies in order to achieve scientifically agreed consensus.

Keywords: Diabetes mellitus; Diabetic ketoacidosis; Length of stay; Sub cutaneous; Pediatric intensive care unit

Introduction

Diabetes Mellitus is a disease resulting from the lack of physiologic effects of Insulin hormone, an anabolic peptide from beta cells of pancreas, genetically linked to human chromosome 11. DM type I, Insulin dependent diabetes mellitus, is associated with certain variants of the *HLA-DQA1, HLA-DQB1, and HLA-DRB1* genes. Due to lack of physiologic effects of Insulin hormone, whether absolute or relative, there is decreased cellular uptake of glucose leading to a severe vicious cycle that may end up clinically as Diabetic Ketoacidosis, DKA. Low cellular glucose levels trigger hyperlipemia, fatty acids enters into beta oxidation metabolism in mitochondria as an alternative energy source leading to increase production of acetyl co-A. Along with other roles in metabolism such as entering in citric acid cycle, acetyl co-A is also a precursor of ketoacids. Its two molecules combine to form acetoacetic acids and then Beta hydrohybutyric acid (Figure 1). Along with insulin deficiency, counter regulatory hormones epinephrine, glucagon, cortisol and growth hormone have important role in the emergence of bio chemical abnormalities of DKA. DKA is one of the serious complications of diabetes in the pediatric population, its prevalence increases by an annual rate of 3% worldwide. It is associated with significant risk of life threatening complications [1-3].

Clinical Presentations and Diagnostic Criteria

The criteria for diagnosis of Diabetic ketoacidosis, DKA in children by the International Society for Pediatric and Adolescent Diabetes describes DKA as blood glucose >11 mmol/L, venous pH <7.3, or bicarbonate <15 mmol/L. The severity of DKA has been categorized as mild (pH 7.21 to 7.3, HCO_3 10 mmol/L to 15 mmol/L), moderate (pH 7.11 to 7.2, HCO_3 5 mmol/L to 10 mmol/L) or severe (pH of less than 7.1, HCO_3 level of less than 5 mmol/L). Depending upon severity, patients can be stable or toxic. New onset DM can present as DKA Children at highest risk for developing DKA include those with previous episodes of DKA, a newly diagnosed DM, poor metabolic control, unstable social situations, noncompliance with insulin, psychiatric and eating disorders, limited access to medical care. Relative to adult diabetics, children with DKA less frequently have underlying infections precipitating their DKA [4,5]. Approximately 69% of young children experience a temporary restoration of beta cell function during first year of diagnosis and initiation of therapy. This is called honeymoon period during which lesser dose of insulin is required [6-8].

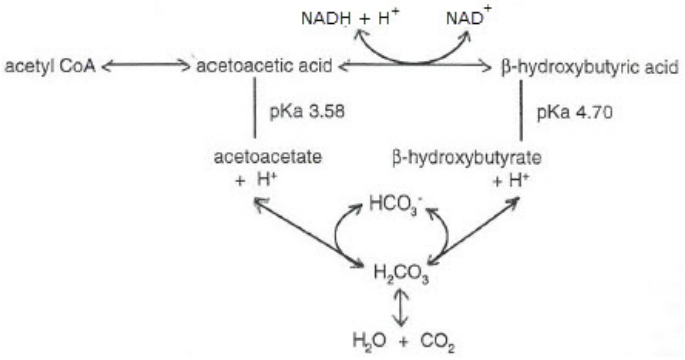

Figure 1: Generation of ketoacids.

Standard DKA Therapy and Variability Considerations

The principal aims of DKA management is to avoid any complications while correcting hydration status and other abnormalities including correction of hyperglycemia, acidosis, ketonemia, treat any precipitating event and avoid complications of management. Patients with DKA should be managed carefully and systematically. Every patient should have a careful history taken and physical examination performed, including weight, Body mass index, vital signs, circulatory and respiratory status, hydration status and level of consciousness. Commence with Airway (avoid intubation), Breathing (provide oxygen), circulation (Intravenous Venous access, avoid central venous catheter, arterial line if indicated, antibiotics (if needed), Urinary catheter (if indicated). Then continue with frequent monitoring, fluid therapy, and insulin regimen and maintain electrolyte balance while carefully watching and preventing complications including cerebral edema, hypoglycemia, hypokalemia, cardiac dysrhythmias, hyperchloremic metabolic acidosis and pulmonary edema. Children are initially are kept NPO (nil per os). Regular feeding can be started once ketones are negative and blood arterial PH is >7.30.

Naeem et al. study

Here in this study children admitted due to DKA. We found that total 197 out of 373 (52%) children diagnosed as DKA were admitted in PICU and rest were managed in Ward. DKA patients admitted in PICU were having severe DKA and had high risks, such as, newly diagnosed DM, patients age <5 years, blood PH <7.10, with severe dehydration, with hypo perfusion or shock, with altered mental status, hypocapnia and high Blood Urea Nitrogen. All the patients were monitored regarding vital signs, neurological assessments including GCS and intake/output, etc. In PICU frequency of monitoring was minimum every hourly while in the ward it was 1-4 hourly depending upon degree of severity of DKA at admission and clinical progress in hospital. Laboratory frequency stayed every 1 to 4 hourly checking of blood glucose, serum electrolytes, BUN, Calcium, Magnesium, Phosphorus and blood gases being more frequent in patients with higher sickness and/or severity of DKA. Patients in PICU received Insulin as infusion (0.05-01 unit/kg/hr) while in the ward rapid acting insulin was administered as q 1-2 hour IV or subcutaneously.

For the calculation of the doses one of two methods were utilized; 1) Total daily requirement calculated based on home regimen and then divided into 12-24 or doses were ascertained from the range of 0.05-0.08 units/kg q1 hr or 0.12-0.15 unit/kg q2 hr while being closely monitored. The initial starting doses were adjusted according to the individual responses There was no difference regarding morbidity and length of stay and zero mortality. None of patients diagnosed as DKA in emergency department was discharged home [9].

Umpierrez et al. study

Upon studying this prospective, randomized, open trial that compared the efficacy and safety of Aspart Rapid acting Insulin (Onset 15-30 min, Peak 30-90) given subcutaneously every 1–2 hourly intervals to a standard low-dose intravenous (IV) infusion protocol of regular insulin. It was noticed that total of 45 patients were randomly assigned to three groups, Aspart given evey hour SC (n=15) in the ward, Aspart given every 2 h (n=15) in the ward, IV regular insulin infusion (n=15) given in the ICU. All three groups had non-significant difference in admission variables. Comparing all three groups, there was no statistical difference regarding duration of treatment for resolution of DKA, LOS, total dose of insulin or any reported complication. Researchers concluded that use of subcutaneous insulin as part every 1 h or 2 h represents a safe and effective alternative to the use of intravenous regular insulin in the management of patients with uncomplicated DKA [10].

Manna et al. study

In this study researcher compared 15 children with DKA receiving fast acting subcutaneous insulin every 2 hour in ED to 30 similar patients who received continuous insulin infusion in PICU in a controlled clinical trial. In the continuous insulin group, metabolic acidosis and ketosis resolved in the first 6-h period whereas in the other group, there was a slower recovery however both groups had no complications and there was a cost-effective and picu sparing benefit that was noticed [11].

Ersoz et al. study

In this prospective, randomized, open trial, hourly subcutaneous (SC) insulin lispro administration was evaluated in comparison with intravenous (IV) regular insulin treatment treating DKA patients. Ten patients were randomly assigned into two groups. Following a bolus injection of 0.15 U/kg IV regular insulin, one group (no=10) received rapid acting insulin while other group (no=10) was kept on IV infusion of regular insulin. They found that time that needed to treat DKA was not different between the groups. In this study, researchers concluded that treatment of mild and moderate DKA with rapid acting SC insulin lispro is equally effective and safe in comparison with IV regular insulin infusion [12].

Balili et al. study

In this recent study researchers evaluated 21 episodes of mild to moderate DKA in adults retrospectively Matched with baseline characteristics, twelve episodes received treatment with continuous insulin infusions while 9 were managed with intermittent rapid acting sub cutaneous insulin. They found no statistically significant difference regarding total amount of insulin administered and total duration of management. There was more frequent occurrence of hypokalemia and longer length of hospital stay in the less cost effective IV insulin group [13].

Discussion

Safe practice according to standards of care

Current guidelines are clear regarding management of children with severe DKA in high risk patients. Regarding management of mild or moderate DKA in children the guidelines along with similar recommendations as management

of severe DKA, with mention of optional practice choices and considerations on individual basis There have been suggestions to revise the guidelines [14-17].

Special considerations for children

In many ways children may pose difficulties for use of intermittent insulin therapy for DKA including psychological, pain perception relevant factors and h presence of honeymoon period.

Cost impacts

Cost of management in PICU settings have many variables affecting the eventual figures such as days of stay in PICU, severity of disease process, original diagnosis, co-morbidities, geographic considerations, types of intensive care settings, etc. Generally there are several reports in literature that describes the cost becomes double or more in intensive care settings [18].

Other effective ways to decrease cost

We should also be considering other strategies including education programs, compliance, new technologies reviews and tutorials. At last, foremost is the maintenance of quality in primary care to maximally enhance usefulness of primary prevention.

Conclusion

There are aspects of DKA management that had been proposed to be revised. As a rule, the maintenance of quality of care and safety should be priority while managing DKA in pediatric patients in PICU versus ward. There shall be a need to keep several basic aspects in considerations including honeymoon phase, uncertain established insulin doses due to variable sensitivity, technical difficulties related to intermittent insulin administration and monitoring, psychological barriers, staff and family education, cost analysis and impacts, life expectancy, presence of co-morbidities, etc. As outset baseline suggestion, pediatric DKA patients for intermittent rapid acting insulin regimen may include children >8 years old, with mild to moderate DKA, established diagnosis and stable insulin regimen for >1 year, Body mass index between 25 to 75 percentiles, absent high risk factors (PCO_2, BUN), no co-morbidities, normal mental status and perfusion and regular preventive care and follow ups. However, future research projects will be essential for the above mentioned considerations.

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