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Review Article

Approach Clinical Management of DKA

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Abstract

Introduction: Type 1 diabetes mellitus is a condition characterize by a lack of insulin actions with unopposed effects of glucagon hormone. Diabetic ketoacidosis (DKA) is considered as acute life-threatening complication of type 1 diabetes mellitus. Nevertheless, DKA may be the initial presentation of the condition. Patient's non-adherence to insulin therapy of failure to administer insulin is at major risk of developing DKA. The condition is precipitated by severe illnesses as pneumonia and myocardial infarction due to elevated levels of hormones opposing insulin (e.g. adrenalin and glucocorticoids). DKA is associated with Acid-Base and Electrolyte imbalance.

Aim of Work: In this review, we are emphasizing the importance of DKA and its pathophysiology with focusing on recommendations for management and treatment strategies based on most recent evidence.

Methodology: We did a systematic search for Approach to DKA using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

Conclusion: Diabetic ketoacidosis (DKA) is a common cause of severe metabolic acidosis. Despite of advances in managements, the condition remains a life-threatening. This is due to complications of the disease and its treatment. This Acid-Base and Electrolyte Teaching Case discusses DKA management, emphasizing complications of treatment. Because cerebral edema is serious complication and is the most common cause of mortality and morbidity, we discussed thoroughly its pathophysiology and the mechanism of preventive approach.

Keywords: *Type 1 Diabetes Mellitus; Diabetic Ketoacidosis (DKA)*

Introduction

Type 1 diabetes mellitus is a condition characterize by a lack of insulin actions with unopposed effects of glucagon hormone. Diabetic ketoacidosis (DKA) is considered as acute life-threatening complication of type 1 diabetes mellitus. Nevertheless, DKA may be the initial presentation of the condition. Patient's non-adherence to insulin therapy of failure to administer insulin is at major risk of developing DKA. The condition is precipitated by severe illnesses as pneumonia and myocardial infarction due to elevated levels of hormones opposing insulin (e.g. adrenalin and glucocorticoids). DKA is associated with Acid-Base and Electrolyte imbalance. In this review, we are emphasizing the importance of DKA and its pathophysiology with focusing on recommendations for management and treatment strategies based on most recent evidence.

Methodology

We did a systematic search for Approach to DKA using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Approach clinical management of DKA.

Discussion

Delaying insulin administration as long as the initial plasma potassium level is 3.3 mmol/L was suggested by the American Diabetes Association and the Canadian Diabetes Association guidelines for DKA management [1,2]. We argue that this level could be too low. As an alternative, we suggest a wiser delay of insulin therapy in case of plasma potassium level of 4 mmol/L. Insulin causes intracellular shifting of potassium, this action is believed to be more pronounced in the presence of academia -as that associated with DKA. The mechanism behind this could be explained by the fact that increased level of hydrogen ion concentration inside cells activates NHE1 (sodium/hydrogen exchanger 1) with subsequent increasing in sodium ion entry into cells and Na1/K1-ATPase activation [3]. Administration of intravenous potassium chloride should be encouraged until monitored plasma potassium is close to 4 mmol/L. Administration of potassium and potassium level should be monitored closely because it is difficult to predict how much potassium will shift into cells. It is worth mentioning that there is no randomized controlled trials to help with such decision in these cases. The intracellular shifting of potassium caused by insulin is rapid and occurs in minutes; on the other hand, the effect of insulin to slow down ketoacid production may take hours. We strongly believe that the risk of exacerbating hypokalemia and subsequent cardiac arrhythmias outweighs the risk of worsening acidemia due to a 1- to 2-hour delay in insulin administration.

DKA patients usually present with a markedly decreased arterial blood volume, this is due to hyperglycemia-induced osmotic diuresis and natriuresis. Adequate amount of fluids (saline) should to be given to achieve hemodynamic stability. However, because of cerebral edema associated with large bolus saline therapy, saline should be given only if hemodynamic emergency is feared. In addition to correcting hypovolemia, fluid therapy aims to increase blood flow to muscles to ensure removal of the hydrogen ion load by bicarbonate buffer system [4]. Buffering of hydrogen ions reduces their binding to proteins in vital organs, such binding may alter protein charge, shape, and possibly functions. The majority of bicarbonate buffer system exists in the ICF and the interstitial space of skeletal muscle and is driven by lower PCO_2 in capillary blood of muscles: H1 1 HCO_3 2 / H_2CO_3/ H_2O 1 CO_2; this mechanism safely removes hydrogen ion. When blood flow to muscle declines due to hypovolemia, but muscle metabolic rate is unchanged, this would result in more carbon dioxide in blood that flows through these hypo-perfused muscles. As a result, and despite of the fact that arterial PCO_2 may be low due to acidemia-induced hyperventilation, PCO_2 in muscle ICF and interstitial fluid may be very high and this could interfere with effective buffering of hydrogen ions by the bicarbonate buffer system. Hence, the degree of acidemia may worsen and more hydrogen ions may bind to proteins in other organs, including the brain. To assess this, brachial venous PCO_2, which reflects capillary PCO_2 in skeletal muscles, should be measured in patients with DKA. Intravenous fluid should be given to increase muscle blood flow to achieve the normal difference of PCO_2 between brachial and arterial blood at normal rates of blood flow and metabolism at rest, w6 mm Hg.

Plasma osmolality should be monitored cautiously and not allowed to decrease in the first 15 hours of treatment, the period that carries the majority of cerebral edema complication [5]. In the first few hours of therapy, a large decline in plasma osmolality that leads to cerebral edema may occur due to the decrease in plasma glucose levels [6]. As sodium anion contribute to plasma osmolality, the aim is to increase plasma sodium level by a half of the decrease occurred in plasma glucose level measured by millimoles per liter. To illustrate this, if initial measurement of plasma glucose was 40 mmol/L and plasma sodium of 130 mmol/L, plasma effective osmolality is (23,130) 1,405,300 mosmol/kg H_2O. If plasma glucose level decreases to 24 mmol/L (a decrease of 16 mmol/L), we would aim for an increase in plasma sodium level of half of this, or 8 mmol/L; this means that plasma sodium level should be raised to 138 mmol/L; by doing this, plasma effective osmolality would be unchanged: (23,138) 1,245,300 mosmol/kg H_2O. Many researchers believe that the increase in

plasma sodium level for a certain decrease in plasma glucose level is predictable and it is due to water movement from the ECF to the ICF. It is worth mentioning that these calculations are based on correlation with assumptions about ECF volume and the volume of distribution of glucose in the absence of insulin. However, patients with hyperglycemia have more variable fluid intake in addition to glucose-induced osmotic diuresis and natriuresis, hence, it is unreliable to assume a similarly fixed relationship between changes in plasma glucose and plasma sodium levels. Thus, using hypotonic saline to avoid the development of hypernatremia during therapy based on these calculations is wrong and may contribute to cerebral edema. By contrast, using fluids with equal or even greater effective osmolality of urine (w400 mosmol/kg H_2O) should be advised in children when they present with DKA and polyuria. This can be achieved by adding potassium chloride (30 - 40 mmol/L to normal saline (0.9% sodium chloride solution) when potassium is needed [5]. Although this could lead to some degree of hypernatremia, we think this is justifiable to prevent a decrease in plasma effective osmolality. In our case, the concern is raised due to patient's consumption of a large volume of water and some may still have been in his stomach and if absorbed, could lead to lower arterial plasma effective osmolality to level that patient's brain would be jeopardized. We inserted an arterial line and monitored plasma effective osmolality in both arterial and venous blood. If critical decrease in plasma osmolality of arterial blood has been noticed, a hypertonic 3% sodium chloride solution should be administered to maintain adequate level of arterial plasma osmolality. This is particularly essential in case of symptoms suggesting increased intracranial pressure as headache, nausea, or obtundation. Calculating the dose of hypertonic 3% sodium chloride solution could be achieved by estimating the current ECF volume and bearing in mind that hypertonic 3% sodium chloride solution has an effective osmolality of close to 1,000 mosmol/kg H_2O. When plasma glucose level decreased to w14 mmol/ L, intravenous glucose should be started to prevent neuroglycopenia. Alternative to the commonly used preparation of glucose (5% dextrose), 50g of dextrose (100 mL of D50W) is added to 1L of 0.9% sodium chloride solution. To replace the sodium loss by natriuresis, enough sodium should be given initially to restore hemodynamic stability and lower the PCO_2 in brachial venous blood to be higher than arterial PCO_2 by 6 mm Hg at most. In addition, correcting the remaining of sodium deficit should be carried on gradually over many hours to minimize the risk for cerebral edema. To avoid excessive administration of saline and excessive expansion of ECF volume, the sodium deficit on presentation should be estimated from the plasma sodium level in addition to quantitative estimate of ECF volume using hematocrit [7]. In general, the aim is to replace w30% of the sodium deficit over the first 4 to 6 hours and correct the remaining deficit over the next 18 hours, together with sodium lost in urine from glucose-induced natriuresis.

Administration of insulin aims to stop ketone acid productions, although this action may take a longer period of time. Again, A bolus of insulin should not be used in children because of the risk for inducing cerebral edema [8]. Nevertheless, the impact of insulin on hyperglycemia early in therapy is minimal because plasma glucose level is decreased initially by dilution and glycosuria. In most cases of DKA, administration of sodium bicarbonate is not needed because insulin will slow the ketoacid production rate, and bicarbonate will be produced when retained ketoacid anions are oxidized. Recommendations and guidelines discourage sodium bicarbonate administration in patients with DKA with the exception when plasma pH is low as 6.90 or less [9]. Only three randomized controlled trials with total of 73 patients have examined the effect of sodium bicarbonate in adults with DKA with exclusion of patients with concomitant serious illnesses. Sodium bicarbonate was found to carry no benefits on each level of outcomes measured including: the change in values of arterial pH, plasma bicarbonate, and measured metabolites. However, one study has reported the possible impact of sodium bicarbonate on mean arterial blood pressure. We suggest the decision to administer sodium bicarbonate should be individualized and not based on arbitrary plasma pH values. Factors that may require administration of sodium bicarbonate include patients with a significant hyperchloremic metabolic acidosis. These patients had excessive loss of ketoacid anions in urine with sodium or potassium and may lack sufficient circulating anions to be metabolized into bicarbonate. Rapid saline infusion may dramatically worsen acidemia in these patients, the mechanism could be explained by dilution and back titration of bicarbonate by hydrogen ions that were bound to intracellular proteins as muscle capillary PCO_2 decreases. Additionally, initial management with sodium bicarbonate could be considered in patients with moderate to severe academia (pH 7.20 and plasma bicarbonate 12 mmol/L) if there is a possibility of lower rate of ketoacid removal. Such possibility raised by a marked decline in consciousness level or in case pf pre-existing chronic kidney disease with glomerular filtration rate of 30 mL/min. Worsening of academia may lead to more severe degree of hemodynamic instability in patients with DKA. Treating these patients with

sodium bicarbonate aids to avoid a significant decrease in plasma bicarbonate level. This should be achieved by administering sodium bicarbonate at similar to expected rate of ketoacid production by the liver. This is estimated to be w60 mmol/per hour based on data from subjects with starvation ketosis [10]. This should be re-evaluated with serial measurements of plasma bicarbonate. It is worth mentioning that there is no clinical trials evaluated the potential benefits of this approach on outcome measures (e.g. restoring hemodynamic stability and the incidence of complications as stroke, myocardial infarction (MI), and acute kidney injury. One retrospective case-controlled study in pediatric patients with DKA found that patients who were treated with sodium bicarbonate had a significantly greater risk for cerebral edema [11]. In our opinion, because harms outweigh benefits, sodium bicarbonate should not be given to children with DKA except if acidemia is very severe (pH 6.90 and plasma bicarbonate 5 mmol/L) and in case of hemodynamic instability that is refractory to administration of intravenous saline [12].

Patients with DKA are usually at catabolic state and may have large phosphate deficits. Plasma phosphate levels decline markedly when insulin treatment begins. However, phosphate administration to promote recovery was not evidenced on data. Nevertheless, hypocalcemia due to precipitation of ionized calcium with phosphate is a dangerous complication to avoid [13]. Current evidence recommends correcting severe hypophosphatemia (serum phosphate of 0.32 mmol/L or lower) particularly in the presence of concomitant illnesses as cardiac dysfunction, respiratory muscle weakness, or hemolytic anemia.

Conclusion

Diabetic ketoacidosis (DKA) is a common cause of severe metabolic acidosis. Despite of advances in managements, the condition remains a life-threatening. This is due to complications of the disease and its treatment. This Acid-Base and Electrolyte Teaching Case discusses DKA management, emphasizing complications of treatment. Because cerebral edema is serious complication and is the most common cause of mortality and morbidity, we discussed thoroughly its pathophysiology and the mechanism of preventive approach. The risk for cerebral edema may be minimized by avoiding a bolus of insulin, excessive saline resuscitation, and a decrease in effective plasma osmolality early in treatment. The essential role of fluid therapy is reducing PCO_2 at the level of muscular veins to ensure adequate removal of hydrogen ions by bicarbonate buffer in muscle that subsequently diminishes the binding of hydrogen ions to intracellular proteins in vital organs including the brain. In patients with relatively low plasma potassium level, rushing in insulin administration may cause hypokalemia and cardiac arrhythmias. Delaying insulin administration and initial administration of intravenous potassium chloride is advised in these patients. The aim is to bring the plasma potassium level close to 4 mmol/L. Sodium bicarbonate administration in adult patients should be individualized and could be considered in specific cases as in patients with moderately severe acidemia who are at risk for worsening acidemia, particularly if hemodynamically unstable. Sodium bicarbonate should not be administered to children with DKA, sever acidemia and cases with refractory hemodynamic instability are exceptions.

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