Review Article

Hyperosmolar Hyperglycemic State Management in the Emergency Department; Literature Review

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Abstract

Hyperosmolar hyperglycemic state is an emergency condition characterized by a significant elevation in blood glucose and serum osmolality level with altered sensorium in the absence of significant ketoacidosis. It is commonly found in the elderly population with poorly controlled type 2 diabetes, but it can also be found in children and adolescents. Early recognition is crucial to establish the precipitating factor and to start proper management immediately. This literature review aims to provide an overview and pathogenesis of hyperosmolar hyperglycemic state and address the necessity of early recognition by the emergency physician and immediate management approach. We searched for relevant articles on the topic in the PubMed database. Common Mesh terms were used: Hyperosmolar hyperglycemic state, emergency management, and complications. The backbone treatment restores the large water deficit and correct electrolyte imbalance induced by severe dehydration. Early identifying the precipitating factor is essential, but not to delay in management. Further instructions must be provided to avoid further attack as HHS has a high mortality rate that reaches 40%.

Keywords: Hyperosmolar hyperglycemic state, Diabetic ketoacidosis, Osmolality, Blood glucose

Introduction

Hyperosmolar Hyperglycemic State (HHS) is a life-threatening syndrome manifested by severe hyperglycemia, hyperosmolality, and dehydration in the lack of ketoacidosis [1, 2]. Most HHS cases are reported in the elderly population, but recently, the incidence among children and young adults has been increased [1]. HHS is observed more commonly in type 2 diabetes (T2D) and occurs in 2% of adolescents at presentation [2, 3]. Nonetheless, HHS can also occur in type 1 diabetes (T1D) [1]. The high sugar beverages consumed by T1D patients secondary to polydipsia could result in high blood glucose and serum osmolality, provoking an HHS, despite T1D pathophysiology [1]. Some small studies report that DKA patients can have HHS features in up to 30% [2].

Although the hospital admission rate for HHS is lower than DKA and less than 1% of all diabetic-related admissions, HHS's mortality rate is higher than DKA, and it can exceed 40%, compared to DKA mortality, which is less than 5% [1, 3, 4]. Previous studies concluded that HHS mortality is higher in females and older patients (above the 60s) and at diabetic onset [1]. Hypothetically, patients with combined HHS and DKA have more critical outcomes than patients with isolated DKA or HHS alone [2]. Concomitant and/or differential diagnose must be evaluated in a patient with HHS, include diabetes insipidus, DKA, myocardial infarction, and pulmonary embolism [4]. Patients with DKA or diabetes insipidus may present with similar HHS symptoms, such as polydipsia and polyuria [4]. Myocardial infarction and pulmonary embolism are risk factors for HHS, and laboratory investigations must be assessed for every HHS patients individually to evaluate for an accurate diagnosis [4]. Other differential diagnoses associated with HHS include infection, pregnancy, and ingestion of drugs such as cocaine [4].

The criteria for HHS diagnosis are (1) Plasma glucose level >33.3 mmol/l, (2) arterial PH ≥ 7.3, (3) serum bicarbonate level ≥ 15 mmol/l, (4) serum osmolality >320 mOsm/kg, (5) decreased level of consciousness or seizure, (6) absence or

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mild ketonuria, (7) absent or mild ketonemia [2]. The old terms, hyperglycemic hyperosmolar nonketotic coma, and hyperglycemic hyperosmolar nonketotic state have been reinstated with HSS [3]. This term replacement reflects that (1) altered level of consciousness may be present without coma and (2) HHS may present with moderate to variable rates of clinical ketosis [3]. Generally, HHS resulted in poorly controlled diabetes and characterized absolute or relative insulinopenia [3]. Elderly and African American ethnicity have increased risk of HHS development [4].

Pathophysiology

The hallmark of HSS pathogenesis is an extreme elevation in serum glucose level and hyperosmolality without significant ketosis [5]. These metabolic disturbances result from synergistic factors, including lack of insulin and increased counterregulatory hormone levels (glucagon, catecholamines, cortisol, and growth hormone) [5]. Following an increase in serum glucose and extracellular osmolality level, an osmolar gradient is formed, which pulls water out of the cells [5]. Initially, glomerular infiltration rate (GFR) increased, which leads to glucosuria and osmotic diuresis [5]. Consequently, this glucosuria prevents the progression of severe hyperglycemia as long as the GFR is normal [5]. Eventually, when osmotic diuresis continued, hypovolemia developed, which leads to a progressive decline in GR and hyperglycemia worsening [5].

In contrast to DKA, a higher hepatic and circulating insulin concentration with low glucagon are present in HHS [5]. The higher circulating ratio of insulin/glucagon in HHS patients prevents ketogenesis and ketoacidosis development, especially that HHS patients have some functioning pancreatic beta-cells [5, 6]. The fluid shift from intracellular to extracellular resulting from osmotic gradients can cause hyponatremia in the early stage of HHS [7]. Nevertheless, the profound dehydration that developed later leads to normalization of serum sodium concentration or even hypernatremia [7]. The osmotic diuresis may lead to loss of potassium, sodium, magnesium, and phosphate through the urine [7].

As a consequence to free water loss over electrolytes, hypovolemia, intracellular and extracellular dehydration, and hyperosmolality develop [7]. Persistent hypovolemia leads to counter-regulatory hormone release, which exacerbates hyperglycemia and contributes to insulin resistance [7]. The total body deficit of water is estimated to be 7 to 12L in HHS, representing a loss of 10% to 10% of total body weight [8]. Although mild ketosis can be present in HHS, it is considered to be absent in this state [8]. Elderly patients with HHS usually have enough insulin to protect them from lipolysis and the consequence abundance of ketoacidosis, but they do not have enough insulin to protect them from hyperglycemia [8].

Results and Discussion

Precipitating Factors

Common HHS precipitating factors include infection, particularly pneumonia and urinary tract infection, neurological events, such as cerebrovascular accident, poor compliance or improper insulin dose, and myocardial infarction [2, 4]. Other factors include pancreatitis, lack of fluid intake, and certain medications associated with metabolic decompensation, such as glucocorticoid, diuretics, phenytoin, thiazide, beta-blockers, and atypical antipsychotics [3-5]. Underlying medical comorbidities, such as myocardial infarction, stroke, and trauma, which promote the release of counterregulatory hormones and/or compromise the fluid intake, may lead to severe dehydration and HHS [5]. In children, HHS is commonly caused by a disease of the nervous, circulatory, and genitourinary systems [5].

History and Physical Examination

The patient's history must include questions that aim to exclude precipitating factors, such as infection, the single most common precipitating of hyperglycemic crisis [9]. Patients with underlying eating disorders may try to withdraw insulin use to avoid weight gain [9]. Also, pregnancy is an insulin-resistant state, and gestational diabetes or pregnancy may prompt a hyperglycemic crisis [9]. Typical hyperglycemic crisis symptoms include polyuria, polydipsia, weight loss, profuse vomiting, and diffuse abdominal pain [9, 10].

Physical examinations must focus on signs of dehydration, poor skin turgor, altered sensorium, lethargy, tachycardia, and hypotension may also present [9]. Altered sensorium can range from full alertness to profound lethargy or coma; additionally, focal neurological deficits (hemianopia and hemiparesis) and seizures (focal or generalized) may also be manifested by HHS [10]. Moreover, the patient may experience fruity, ketotic breath smell, Kussmaul breathing, which is a deep, labored breath indicative of a hyperventilation reaction to metabolic acidosis, but is often present in patients with DKA [9]. The progression of HHS usually develops over several days to weeks, while the evolution of DKA usually takes much shorter [10].

Management of HHS

Intravenous Fluid Replacement

HHS's dominant feature is hyperosmolality, which results in massive electrolyte deficits of sodium, potassium, and chloride [11]. HHS's primary treatment is to correct fluid, electrolyte deficits, and insulin therapy over the first 24-48 hours to replete extracellular fluid volume and restore intravascular volume [11, 12]. Recognizing the precipitating cause of HHS is crucial, but this should not lead to any management delayed [12]. Optimal fluid administration not only replaces intravascular volume but also decrease serum glucose, stabilize blood pressure, secures peripheral tissue perfusion, and promotes metabolic acidosis resolution [12]. The choice of a fluid replacement should consider factors such as age, gender, rate of hydration, and patient history,

e.g., cardiac disease [11]. Isotonic saline (0.9% NaCl) is seen as the initial replacement by most experts [11, 12].

The American Diabetes Association (ADA) recommends replacing 1000-1500mL, while the UK guidelines recommend 1000mL of normal saline over the first one hour [12, 13]. The suggested volume of replacement after that is 10-20 mL/kg/h, and the American Diabetes Association (2003) is 15-20 mL/kg/h [11]. The ADA Suppose the patient developed hypovolemic shock (systolic pressure <100 mmHg), then intravenous colloid should be admitted [11]. In mild to moderate depletion, rates of 7 ml/kg/h have also shown the wanted outcome [11]. According to the American Diabetes Association (2003), serum osmolality should not decrease by >3 mOsmol/kg H2O/h [11].

Improper use of fluid resuscitation can cause an increased serum sodium concentration and a further increase in plasma osmolality, leading to pontine myelinolysis [11]. The abrupt falls in sodium level can cause cerebral edema [11]. Therefore, a decreased intravenous fluid rate is recommended in older patients and those with cardiac disease and concomitant mild DKA [11]. To avoid fluid overload complicated by iatrogenic fluid replacement, frequent cardiac, renal, and mental status is recommended by the American Diabetes Association [11]. Attention should be taken if blood pressure stability is not reached after 2 hours of fluid replacement [11].

If the corrected serum sodium increased over 155 mmol/L, 0.9% NaCl should be replaced with 0.45% NaCl [11]. The American Diabetes Association (2003) advises a rate of 4-14 mL/kg/h of 0.45% NaCl if the corrected sodium is normal or raised [11, 13]. The choice of 5% glucose or glucose saline must be considered if the blood glucose level drop below 13 mmol/L [11]. Also, it suggested doubling the dose of insulin if the glucose level is not dropping by 2.8-3.9 mmol/L/h (50-70mg/dL/h) [13]. NaCl 0.9% can be continued at a slower rate for rehydration and electrolyte replacement; however, administration of 5% glucose can be continued until ketonemia is controlled and iatrogenic hypoglycemia is avoided [11, 12].

Potassium and Phosphate Replacement

In HHS, no studies have tested the optimal approach to hypokalemia and hypophosphatemia treatment [12]. Nonetheless, HHS patients typically have more sere body depletion than DDK, and close monitoring is recommended [12]. Therefore, it is essential to test the serum potassium level before insulin administration, as it can cause a further drop in extracellular potassium level [14]. The ADA recommends potassium replacement of 20-30 mmol in each liter of fluid infusion when serum potassium is below 5.2 mmol/L [12]. Phosphate level can be impaired in patients with HHS, and therefore, it should be routinely tested [14]. Phosphate level is not routinely commended unless levels are dropping below 1.0 mg/dL, and patients experienced signs of cardiac compromise or hypoxia [14]. The UK guidelines recommend phosphate replacement if persistent hypophosphatemia occurred beyond the acute phase of HHS treatment [12].

Insulin Administration

When to initiate insulin administration in HHS management, the inquiry of when to initiate insulin administration has not been formally investigated [12]. The ASA guidelines recommend initiating regular intravenous insulin in the same approach as DKA management [12]. Intravenous regular insulin must be started at either a fixed weight-based dose of 0.14 units/kg/h or at a fixed weight-based dose of 0.1 units/kg/h followed by 0.1 units/kg bolus of insulin intravenously after initiating of fluid administration and correction of hypokalemia if any [12]. Intravenous insulin administration is recommended due to the prolonged half-life compared to the subcutaneous route [14].

Nonetheless, some guidelines recommended a bolus dose of insulin subcutaneously [14]. Administration of insulin will help restore glucose homeostasis by entering high glucose in the blood into the cells and decreasing hepatic glucose production in case of concomitant mild ketoacidosis [14]. Generally, low-dose insulin is recommended because most protocols advocate aggressive fluid resuscitation immediately before or during insulin commencing [14]. Initially, during HHS management, blood glucose may not decline as renal impairment may coexist or inadequate fluid resuscitation rather than insulin resistance [14]. Hence, adequate fluid replacement and monitoring of urea and creatinine levels are crucial when assessing insulin therapy's efficacy [14].

Complications of HHS Management

Cerebral Edema

Cerebral edema is rare, but serious adverse effects on hyperglycemic crisis management [12, 15]. It has been reported most frequently in children and adolescents with DKA as the first presentation of T1D, carrying a mortality rate between 20-40% [12, 15]. It has been rarely reported in adults more than 28 years, and current recommendations advised to maintain blood glucose level no lower than 13.9-16.6 mmol/L (250-300 mg/dL) for several hours during the initial course of treatment [12]. The exact pathophysiology of cerebral edema is incompletely understood, but it is thought to be related to disruption of the blood-brain barrier found in some cases of fatal cerebral edema [15]. It usually developed 4-12 hours after treatment initiation, but it may develop late as 24-48 hours after the start of treatment [15].

Symptoms suggestive of neurological deterioration must be identified early, such as headache, decreased level of consciousness, recurrent vomiting, incontinence, irritability, abnormal respiration pattern, delayed rise in serum sodium level with treatment, or evidence of cranial nerve dysfunction [12]. Immediate administration of mannitol therapy at a dose of 0.5-1g/kg over 20 minutes can support to eliminate further neurological deterioration [12]. A cranial CT scan should be performed after starting cerebral edema treatment to rule out

other possible etiologies of neurological decline, particularly cerebral infarction, thrombosis, hemorrhage, or dural sinus thrombosis [15]. Bicarbonate treatment has the potential risk of provoking cerebral edema as well as hypokalemia [16].

Electrolytes Disturbances

More frequently observed adverse treatment effects in adults include hypokalemia, hyperkalemia, hypoglycemia, and non-anion gap hyperchloremic metabolic acidosis [12]. Hypoglycemia is the most expected adverse outcome during treatment, and it is associated with both immediate and late adverse clinical outcomes [15, 16]. Adverse outcomes include seizure, arrhythmias, altered sensorium, and cardiovascular events (myocardial infarction and stroke) [15, 16]. The contribution of hypoglycemia to adverse cardiovascular outcomes remains questionable [16]. This was concerned following publications of large clinical trials that concluded no reduction in cardiovascular disease events among patients treated intensively with T2D [16].

Hypokalemia is the second most common adverse outcome of HHS management [15]. Although the serum potassium is elevated upon admission, during insulin therapy, plasma potassium level sill invariably dropped secondary to increase cellular potassium uptake in peripheral tissues [15]. Therefore, IV potassium replacement is recommended when concentration falls below 5.2 mEq/L [15]. In patients admitted with serum potassium below 3.3 mEq/L, IV potassium replacement should be commenced immediately at a rate of 10-20 mmol/h and hold insulin therapy until potassium level is more than 3.3 mEq/L to avoid severe hypokalemia [15, 16].

Rhabdomyolysis

Rhabdomyolysis occurs more commonly in HHS than DKA resulting in an increased risk of acute kidney injury [15]. The typical symptom triad includes myalgia, weakness, and dark urine [15]. Monitoring creatinine kinase level every 2 to 3 hours is recommended for early detection [15].

Conclusion

The hyperosmolar hyperglycemic state is a serious complication of poorly controlled diabetes which carries a high mortality rate that reaches 40%. The classical features are severe hyperglycemia, hyperosmolality, electrolytes disturbances, and dehydration in the absence of ketoacidosis. HHS is more commonly present in elderly patients with type 2 diabetes mellitus. Still, it can be present among children and young adults. HHS is typically diagnosed by raised blood sugar concentration and serum osmolality, normal arterial PH and bicarbonate level, altered level of consciousness with absence or mild ketonuria. Certain factors usually precipitate HHS, and recognizing them is essential to prevent further episodes. The mainstay of treatment is intravenous fluid replacement, insulin therapy, electrolytes correction, and manage the underlying precipitating factor. There is no specific protocol for treating HHS, but the approach is usually similar to DKA management. Caution must be taken to the adverse management effect, such as cerebral edema, electrolyte imbalances, and rhabdomyolysis.

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