Review

Dyselectrolytemic Emergencies in Oncological Patients: A Brief Review

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Electrolyte imbalance in cancer patients is frequently reported. The etiopathogenesis of dyselectrolytemia in cancer patients is multifactorial. The tumor itself, secreting hormone, altered intake, altered hypothalamic pituitary adrenal axis, renin angiotensin aldosterone axis, renal dysfunction, rearranged acid-base and fluid status, chemotherapy drugs, etc., can impact the electrolyte homeostasis in oncologic patients. Further, syndrome of inappropriate antidiuretic hormone (SIADH), tumor lysis syndrome (TLS), and paraneoplastic syndrome are well-reported clinical constellations that present with significant electrolyte imbalances and can even be life-threatening. Even co-morbid conditions of the patient can impact electrolyte homeostasis. [1,2] Dyselectrolytemia in cancer patients impacts the initiation and continuation of treatment and performance status and even negatively affects the outcome.[1] Although dyselectrolytemia for almost all electrolytes can be found, and in different severity, not all dyselectrolytemia leads to medical emergencies. The present brief write-up is intended to serve as a ready reference for the dyselectrolytemia in cancer patients, which can present as an emergency and their brief management principles.

Pathophysiologic basis

The pathophysiologic basis of electrolyte imbalances in cancer patients is multi-dimensional. The fluid and electrolytes are interdependent, and feedback mechanisms, hormone levels, and organ functions maintain balance. These mechanisms can be directly or indirectly involved by the cancer cells, paraneoplastic syndromes, and chemotherapy-related cellular lysis.[3] The human body regulates fluid and electrolytes through the hypothalamic-pituitary-adrenal axis, where different stimuli can upregulate or downregulate the axis functionality. The axis is also involved in the functionality of the hepato-biliary and gastrointestinal systems, major organ systems involved in the absorption and secretions of different electrolytes. Further antidiuretic hormone and the renin-angiotensin-aldosterone axis play a significant role in fluid balance, affecting electrolyte concentrations.[4]

The human body has different compartments based on cellular level fluid location. It can be grossly divided into, i.e. intracellular and extracellular compartments. On the other hand, the extracellular compartment can again be divided into interstitial and plasma compartments.[5] Although we divide them into different compartments, they work in unison, and derangement in the fluid and electrolytes in one compartment can affect the other by impacting the fluid movement. The fluid movement from one compartment to another is governed by the number of osmotically active solutes among the compartments. Only osmotically active solutes that cannot freely diffuse across the semi-permeable membrane exert effective osmotic pressure and are responsible for osmosis, i.e., water movement across the membrane into the solute-containing compartments. Among such solutes, Na and K play an important role, especially the sodium level, as the concentration of Na is relatively very high compared to the K concentrations.

Further, Na balance is primarily responsible for volume regulation, and any change in the plasma (extracellular compartment) Na concentration will affect the volume regulation. Osmoregulation and volume regulation work in synergy to maintain fluid and electrolyte homeostasis. Plasma osmolality change stimulates the hypothalamic osmoreceptors and regulates ADH and thirst, resulting in water volume changes. On the other hand, changes in the water volume cause changes in the effective circulatory

volume or perfusion, which is sensed by the baroreceptors and macula densa, regulates the sympathetic systems, RAAS, ADH, natriuretic peptides, and pressure natriuresis resulting in the changes in the Na excretion.[6]

The sodium levels in cancer patients can be affected by chemotherapeutic agents like vinca alkaloids, platinum analogues, and even immunomodulators like interleukin-2 and interferons.[7] These drugs affect the ADH regulation system and cause SIADH. Even renal salt wasting, ectopic ADH secretion, and pain and pain medication-related stress and ADH imbalance are responsible for Na imbalances in cancer patients.

The kidney regulates Potassium homeostasis significantly and is dependent on intake, hormone levels, and acid-base status. In cancer patients, hypokalaemia might be caused by low intake (loss of appetite), a higher loss like vomiting, diarrhoea, higher use in increased hematopoiesis as in hemato-oncology cases, and even increased mineralocorticoid activities. On the other hand, increased cellular lysis (tumor lysis), renal tubular acidosis (Type I), and some drugs can cause hyperkalemia. Both hypo and hyperkalemia can affect the cardiac physiology causing arrhythmias.

Incidence

In terminal cancer patients admitted to the palliative care unit, the incidence of dyselectrolytemia on admission was 67.74%.8 Another study analysing data from nearly 26,000 hospitalized patients diagnosed with malignancy noted at least one dyselectrolytemia in 58%.[9]

Electrolyte and acid-base imbalance incidence rates vary among the different types of malignancies. Study indicates that leukemia, gastrointestinal malignancies, and cancer involving the central nervous and renal system have higher incidences of electrolyte and acid-base imbalances .[9]

Common dyselectrolytemias

Usually, low electrolyte levels are a common phenomenon at higher levels. A study analyzing a large number of patients indicates that hypocalcemia is the commonest dyselectrolytemia noted, with an incidence of 27.8%. Other common electrolyte imbalances are Hypophosphatemia (26.7%), Hypochloremia (24.4%), Hyponatremia (22.5%), Hypokalemia (14,9%), hyperphosphatemia (14.7%), and Hypermagnesemia (10.0%). While hypercalcemia is found in 2.8% of cancer patients, the incidence of hypernatremia and hyperkalemia is only 1.5 and 1.0%, respectively.[9]

Like the variable incidences, the type of electrolyte imbalances also varies in different types of cancers. Nearly 40-70% of the hepatic-biliary, pancreatic, gastrointestinal, and leukemia patients present either hyponatremia, hypokalemia, and hypocalcemia or in combination. Although the overall incidence of hypernatremia is low, nearly 10% of CNS cancer patients might have hypernatremia or hypercalcemia. On the other hand, gastric and female genito-urinary cancer patients also have a high incidence of hyperchloremia.[9]

Factors affecting

Cancer patients having severe illness, dehydration, and on opioid therapy were at risk of dyselectrolytemia.[8] Higher age, cachectic patients, patients requiring nutritional supplements due to poor intake, having comorbidities, and receiving chemotherapy has higher odds of having dyselectrolytemia.[10]

Overview of Management

Although almost all electrolytes can be affected throughout cancer illness, some of the dyselectrolytemia can be immediately life-threatening, requiring immediate intervention. Hypernatremia, Hyponatremia, and Hyperkalaemia are a few common dyselectrolytemia that can present as emergencies.

Hyponatremia

A thorough assessment of the patient's medical history, physical examination, and laboratory tests, including urinary chemistries and serum and urine osmolality, is necessary to determine the root cause of imbalance; pseudo hyponatremia needs to be ruled out, and the volume status of the patient needs to be assessed before determining the treatment. The chronicity of hyponatremia also impacts symptomatology, and acute and significant changes lead to headaches, nausea, confusion, seizures, hallucinations, and coma. Severe hyponatremia (<110 meq/L) or patients with neurological symptoms needs urgent attention and invariably need to be treated with hypertonic saline (usually 3% NaCl) supplementation [11]. Fluid management is dependent on the volume status. While hypervolemic cases can be managed with fluid restrictions, hypovolaemic cases are challenging and must be supplemented with fluid; a balanced salt solution can be used. Fluid therapy should be cautious in patients with underlying cardiac pathology or failure.

The rapidity of the hyponatremia correction also depends on symptoms and acuteness; acute cases with neurological

symptoms should receive 3% NaCl infusion to correct 4-6 meq/L over 4-8 hours.[12] Nevertheless, total correction over 24 hours should not exceed 10meq/L and is usually targeted for 8 meq/L rise in the first 24 hours, 6 meq/L in the next, and 2-4 meq/L during 48-72h.[12] Total correction over 72 hours should be lower than 20 meq/L. Otherwise, it can still cause myelinolysis.[13,14] Mild and asymptomatic hyponatremia can be treated with dietary supplements of NaCl or tablets.

Hypernatremia

Like hyponatremia, hypernatremia also needs a thorough assessment of the patient's medical history, physical examination, and laboratory tests. It can be hypovolamic, euvolemic or hypervolaemia. Urinary sodium level helps in determining the aetiologies among these categories. Hypernatremia is usually classified as moderate if the serum Na level is 150-169 mmol/L and severe when the level is $\geq$ 170 mmol/L. Getting paired serum and urine osmolality is advisable in moderate to severe hypernatremia. However, treatment should be completed on time to get the reports. While chronic hypernatremia (slowly rising Na levels over >48h) is usually well tolerated by the patients, acute moderate to severe hypernatremia usually causes neurological signs and symptoms owing to its effect on the brain matter and vasculature. Mild hypernatremia usually presents with vague symptoms. The thirst mechanism usually protects the body from developing moderate and severe hypernatremia. However, poor intake, nausea, vomiting, and altered hormonal levels can predispose to severe hypernatremia in cancer patients. Altered mental status, seizure, hyperreflexia, and coma are present in severe hypernatremia.

Acute severe hypernatremia is a medical emergency requiring immediate intervention to restore serum tonicity by reducing serum Na levels. It is done by supplementing water deficits in a calculated manner. Hypernatremia in cancer patients is usually slow in onset, and correction of the water deficit in such cases should be slower. On the other hand, if the hypernatremia has developed over hours, rapid correction is advised. Water deficit must be calculated from the current body water and serum Na levels. Body water, in turn, depends on the gender and even age of the patients.[15,16] Although isotonic saline (0.9% NaCl), to some extent, can be used for restoring the circulatory volume, it is unsuitable for correcting hypernatremia, and hypotonic NaCl is usually used.[17] Nevertheless, the correction should be titrated to prevent cerebral edema and convulsions. The advised rate of correction for slow-onset hypernatremia is 0.5 meq/L per hour and one meq/L per hour for sudden-onset hypernatremia; the maximum correction should not exceed 12 meq/L per 24h .[17,16]

Hyperkalaemia

Hyperkalaemia is defined as serum K level >5.5 meq/L. Unless there is a renal dysfunction where excretion of the K is defective due to renal pathology, drug therapy, or renin-aldosterone axis abnormalities, hyperkalemic states are usually transient. However, serum K >6.5 meq/L or hyperkalemia causing electrical disturbances of the heart, as evidenced in the electrocardiogram, is potentially life-threatening and needs emergency attention. Pathophysiologically, hyperkalemia can be due to excessive intake, reduced excretion from the kidney, and transcellular shift (intracellular to extracellular).[19] Acutely increased serum K level causes an imbalance of the potassium concentration gradient in myocytes and other myocardial structures, causing electrophysiological changes and arrhythmias.

Detailed history, physical examination, and laboratory tests can help find hyperkalemia's aetiologies. Nevertheless, such diagnostic workups should not defer the management of acute symptomatic hyperkalemia. Treatment of hyperkalemia is based on stabilizing the cardiac cellular membrane by administering calcium. Calcium chloride 1g or calcium gluconate 2g is infused over 5 minutes and repeated every 5-10 minutes if ECG changes persist. The duration of action is only 30 to 60 minutes. Therefore, if the patient is not on continuous ECG monitoring, a repeat ECG should be obtained every 1 hour of the first dose. The next step of hyperkalemia treatment is shifting the extracellular K to the intracellular level, which is done by infusing glucose-insulin solution, beta-agonist nebulization, and sodium bicarbonate administration. The usual dose of glucose-insulin is ten units of regular insulin for 50gm of glucose. However, glucose should be avoided if the patient's blood sugar level is >250 mg/dL. Further, although 100 mL D50 (50% dextrose) is the advised solution, the concentration and fluid amount can also be modified based on the patient's volume status. Nevertheless, many a time, such patients have acute or chronic renal failure, and solutions with limited volumes are preferable. Routine use of sodium bicarbonate solution is not advisable but can be considered if the patient is acidotic; 50 meq of sodium bicarbonate is administered over 5 minutes. The third step is eliminating the K from the body; loop diuretics, intravenous fluids, exchange resins, and dialysis can achieve this. While exchange resin like oral or rectal sodium polystyrene sulfonate can work in renal failure patients, loop diuretics and intravenous fluids may not be suitable in anuric patients. In such cases, definite

management for eliminating the excess K is dialysis. Further, dialysis is also indicated if the above medical management fails.

Tumour lysis syndrome

It is a common emergency in hematological cancer patients with significant electrolyte imbalances. It is commonly noted in non-Hodgkins' lymphoma and acute leukemia, frequently after starting chemotherapy, and characteristic findings of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia.[20] Initial presentation is related to the acute acid-base and electrolyte imbalance and can manifest as tetany, arrhythmias, seizure, and cardiac arrest. Later in the course, patients usually have acute kidney injury and multi-organ failure. The severity of the presentation depends on the tumor mass, lysis potential of the tumor cells, and characteristics of the patients, like chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine.[20,21]Inadequate fluid therapy during the chemotherapy also predisposes patients to severe tumor lysis syndrome.

The management of TLS is targeted to prevent acute kidney injury, prevention, and treatment of arrhythmia and tetany. AKI in TLS is also related to crystal-induced tissue toxicity, increasing urine output by hyperhydration. If hydration therapy does not achieve the urine output target of 2mL/Kg/hour, loop diuretics are advised to achieve the target. Further, as uric acid plays a significant role in TS-related AKI, preventing uric acid by allopurinol and breaking the uric acids by rasburicase is also effective in preventing AKI development. Hyperkalemia is the most dangerous component leading to life-threatening arrhythmias, and management should follow the principle of stabilizing the cardiac cellular membrane, shifting the extracellular K to the intracellular level, and eliminating the K from the body, as described above. Hypocalcemia can also cause life-threatening arrhythmias and tetany. Hypocalcemia of TLS is treated only if symptomatic and should be managed using calcium gluconate or calcium chloride in minimal effective (titrated dose) to stop the arrhythmia and tetany. Although there is no robust beneficial effect of treating hyperphosphatemia, phosphate binders can be used. Early hemodialysis should be considered if the patient has already developed severe AKI or arrhythmia and tetany is not responding to medical management.

Dyselectrolytemia is common in cancer patients. Patients with comorbidities, poor intake, dehydration, and poor physical status are at high risk of developing dyselectrolytemia. Higher tumor mass, hemato-onco patients, hepatobiliary, and gastrointestinal cancer patients have higher chances of having electrolyte imbalance. Severe sodium and potassium imbalance can cause acute life-threatening crises. A Thorough assessment of the patient's medical history, physical examination, and laboratory test can help us get the etiology, but emergency management should not be delayed in establishing the etiologies.

Conflict of interest: Nil

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