Informative Article

Lactic Acidosis In Critically Ill Patients

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Abstract:

Lactic acidosis is defined as increase in blood lactate levels in association with acidemia. It should be suspected in all patients presenting with shock & decreased mayocardial contractility. The patients with lactic acidosis have high mortality. However, the prognosis and case fatality are completely dependent on underlying disease in each patient with lactic acidosis being an independent indicator of severity of shock. All efforts should be directed towards treatment of underlying cause and concomitant correction of acidosis.

Key Words: Lactate, Pyruvate, Lactic acidosis,THAM.

History:

Lactic acidosis was first described in literature in the year 1920. Clausen in the year 1925 identified accumulation of lactic acid as a cause of metabolic acidosis. However, till the year 1960 it was not recognized as significant clinical problem. In year 1976, Cohen & Woods classified lactic acidosis on the basis of presence or absence of adequate tissue oxygenation. Lactic acidosis is the most common under diagnosed life threatening form of metabolic acidosis present in 0.5% to 3.8% critically ill patients.

Definition:

Lactic acidosis is a pathological state diagnosed when the serum concentration of lactate or lactic acid is persistently 5mmol/L or greater and there is significant acidemia and serum pH< 7.35. (Normal lactate concentration is 2.0 mmol/L).

Formation of Lactic acid:

There is constant production and metabolism of lactate in the body. Red blood cells, brain and skin are major sources of lactic acid at rest while during exercise skeletal muscles release significant amount of lactic acid.

Kidney and liver utilize lactic acid and convert it into carbon dioxide and water and use it for gluconeogenesis. Normally there is fine balance between lactic acid production and utilization.

Lactic acid and pyruvic acid are inter convertible and the reaction is catalyzed by the enzyme lactate dehydrogenase in the presence of Nicotinamide Adinine Dinucleotide / Nicotinamide Adinine Dinucleotide Phosphate (NAD/NADH). (The normal ratio of lactic acid: pyruvic acid is 10:1).

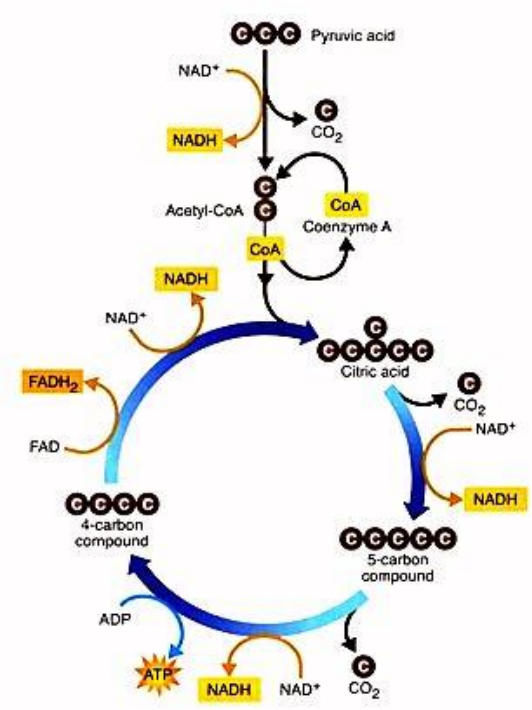

Fig.I: Kreb's cycle showing formation of lactic acid.

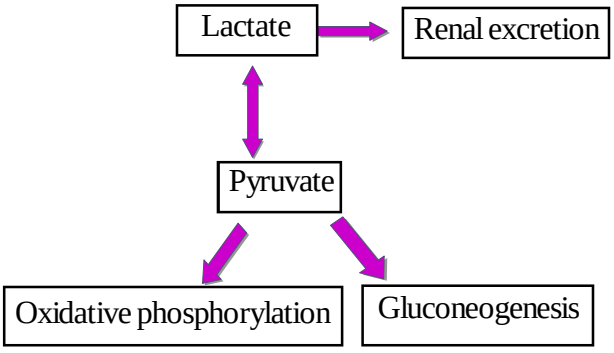

Fig. II: Metabolic fate of lactic anion.

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Classification of Lactic Acidosis (Cohen & Woods):

They classified lactic acidosis into two types- Type A and Type B.

TYPE A: It occurs in hypoperfusion and hypoxia.

- *Tissue hypoxia* is seen in carbon monoxide poisoning, severe asthma and severe anemia.
- *Hypoperfusion* occurs in state of shock (cardiogenic, hemorrhagic, septic, regional ischemia)

TYPE B: It occurs when there is no clinical evidence of hypoperfusion. It is further subdivided into 3 subtypes:-

(i) B1is associated with acquired diseases like diabetes mellitus, grand mal seizures, hepatic failure, septicemia, malignancies, pheochromocytoma, post cardiopulmonary bypass, renal failure, thiamine deficiency, thyroid storm etc.

(ii)B2 is associated with metabolites, drugs and toxins like acetaminophen, biguanides, cocaine, diethyl ether, epinephrine, norepinephrine, ethanol, ethylene glycol, isoniazid, lactulose, methanol, nalidixic acid, niacin, nitroprusside, antiretroviral therapy, paraldehyde, parenteral nutrition, terbutaline, theophyline etc.

(iii)B3 is due to inborn errors of metabolism (congenital lactic acidosis) e.g. Glucose-6 phosphate dehydrogenase deficiency, fructose1-6 diphosphatase deficiency, pyruvate carboxylase deficiency,organic aciduria, Leigh's disease, Alpers disease and mitochondrial encephalopathies etc.

Miscellaneous:

Spontaneous lactic acidosis or idiopathic lactic acidosis like chronic recurrent lactic acidosis may be due to subclinical, regional hypoperfusion or coexistence of various predisposing conditions or late manifested enzymatic defect.

D-lactic acidosis is rare and is caused by d-stereo isomer of lactic acid (d-lactic acid) which is synthesized by pathological gut flora. It can not be measured by standard lactate assay method.

Clinically important causes of lactic acidosis are overproduction or underutilization of lactate or both the conditions co-existing together.

1. Vigorous exercise: The magnitude of increase in lactic acid concentration depends upon the type and severity of exercise. Same is also true following prolonged generalized tonic clonic seizures (GTCS). Lactate level falls to normal immediately following cessation of exercise or GTCS due to rapid metabolism of lactic acid or its diffusion in to total body fluid. This is associated with fall in bicarbonate concentration, which rapidly returns to normal once GTCS subsides. As the acidosis is abrupt and transient, secondary response of hyperventilation may not develop and even if magnitude of acidosis is high, bicarbonate therapy is not required.

2. Tissue hypoxia: It is the predominant cause of lactic acidosis in critically ill patients. Prolonged hypoxia will lead to overproduction and underutilization of lactic acid leading to lactic acidosis. Patients with hypotension either due to septic, hypovolumic or cardiogenic shock, may develop lactic acidosis due to poor perfusion of skeletal muscles and overproduction of lactic acid. The degree of lactic acidosis correlates well with the duration and severity of shock and is a prognostic factor in the survival of the patients.

3. Cardio-respiratory arrest: It is another cause leading to severe acidemia due to combined lactic acidosis and respiratory acidosis due to cardiac arrest and respiratory arrest respectively. Similarly patients with acute left ventricular failure with pulmonary edema may develop acidosis due to reduced tissue perfusion and respiratory acidosis due to respiratory failure. Reduced partial pressure of oxygen (PaO_2) seldom causes lactic acidosis if cardiovascular status is normal because it is compensated by increased tissue perfusion. In patients of type II respiratory failure secondary to advanced chronic obstructive airway disease, seldom have lactic acidosis if there are no other confounding factors. It is due to the fact that these patients have chronic compensated respiratory acidosis and PaO_2, is reduced.

4. Carbon monoxide poisoning: It typically produces lactic in the form of acidosis due to lack of compensatory mechanism of increased tissue perfusion. Carbon monoxide binds to hemoglobin and as its affinity for hemoglobin is 40 times more than that of oxygen, it leads to tissue hypoxia and lactic acidosis.

5. Drugs and toxins: Some of drugs & toxins also lead to increased production of lactate. Alcohol ingestion is a common cause of lactic acidosis as ethanol oxidation increases the conversion of pyruvate to lactate and decreases the clearance of lactate.

Alcohol induced lactic acidosis is treated by correcting the hypoglycemia and electrolyte imbalance. Alkali therapy is rarely required in such cases. Prolonged metformin therapy is associated with lactic acidosis for many reasons. It increases glycolysis in peripheral tissues, decreases pyruvate oxidation and reduces hepatic lactate clearance.

Many other drugs may also lead to lactic acidosis but it is not certain whether these drugs per se or associated hypotension produces lactic acidosis. Fructose, frequently used in intravenous fluids and total parentral nutrition, leads to deficiency of thiamin and accumulation of lactate. It also leads to inhibition of lactate utilization by liver and hence produces lactic acidosis. Sorbitol also gets converted into fructose and leads to lactic acidosis by the same mechanism.

Epinephrine enhances hepatic glycogenolysis and glycolysis to lactate and reduces pyruvate utilization resulting in lactic acidosis especially in massive doses. Septic patients because of hypotension and poor peripheral perfusion are at risk of developing lactic acidosis.

6. Terminal cirrhosis or hepato-cellular failure: It may lead to lactic acidosis due to poor utilization of lactate and altered metabolism.

7. Neoplastic diseases: Leukemia predisposes to lactic acidosis because of production of large amount of lactate by tumor cells and it resolves gradually after the successful treatment.

8. Congenital deficiency of enzymes: Enzymes which are involved in gluconeogenesis (glucose-6 phosphate dehydrogenase, fructose 1, 6 pyruvate carboxylase), pyruvate oxidation (Pyruvate dehydrogenase) and key enzymes of oxidative phosphorylation may also lead to development of congenital lactic acidosis.

Clinical symptoms of lactic acidosis: Symptoms are non specific and are those of underlying primary disorder. Lactic acidosis should be suspected in all critically ill patients who are hypovolumic, hypoxic, in septic or cardiogenic shock or if unexplained high anion gap metabolic acidosis is present.

Clinical signs consistent with tissue hypoperfusion (peripheral vasoconstriction), hypotension, oliguria/ anuria and altered sensorium are usually present in patients of lactic acidosis.

Diagnosis:

The major clues leading to the diagnosis of lactic acidosis includes:

- Increased anion gap (AG) metabolic acidosis
- Increased level of serum lactic acid (> 5 mmol/ L by enzymatic method)
- Significant acidemia (arterial pH< 7 .35)
- Decrease in plasma bicarbonate.

Laboratory studies include: Arterial blood gas analysis (ABG), calculation of anion gap (normal range of anion gap is 10-12mmol/L), serum lactate assay (for serum lactate assay sample must be transferred in ice filled pack and analyzed within 4 hours- reference range for serum lactate is < 2mmol/L).

Diagnosis of lactic acidosis may be missed in patients with uremia and concomitant metabolic alkalosis if the clinical suspicion is not high.

One should always obtain plasma lactate levels in patients with acute respiratory failure when ever bicarbonate concentration falls unexpectedly which may not be explained by respiratory failure alone.

In patients with lactic acidosis with concomitant metabolic alkalosis, the clue to the diagnosis is unexpected increase in anion gap.

Differential diagnosis includes the common causes of increased anion gap acidosis like renal failure, diabetic ketoacidosis and rhabdomyolysis. They may occur alone or co-exist with lactic acidosis

Treatment: The most important therapy in management of lactic acidosis is correction of underlying cause. In hypovolumic or cardiogenic shock, restoration of perfusion and adequate tissue oxygenation will reverse lactic acidosis. In septic shock, antibiotic treatment, surgical drainage/debridement will help in reversal of lactic acidosis. Giving intravenous thiamine in cases of total parentral nutrition will help in resolution of lactic acidosis. In status asthmaticus, high dose of beta 2 agonist should be tapered gradually to reduce lactate levels. In shock, vaso constrictors should be added only after volume replacement as they worsen the acidosis.

Alkali Therapy though theoretically appealing, but only few studies document safety and efficacy of bicarbonate in lactic acidosis. Correction of acidosis

with bicarbonate may reverse depressed cardiac performance in critically ill patients. The side effects of bicarbonate therapy is acute hypercapnia which increase intracellular acidosis and ionized hypocalcemia which in turn decreases the myocardial contractility. Bicarbonate is a hypertonic solution and causes volume overload and cardiac depression. It also increases the lactate production by increasing the activity of rate limiting enzyme phosphofructokinase. Adverse effects of bicarbonate can be reduced by giving slow infusions in preference to rapid boluses, by increasing minute volume in patients on ventilator and by correcting hypocalcemia. Bicarbonate therapy is useful in patients of ischemic heart disease as acidosis increases the risk of major arrhythmias due to lowering of the myocardial threshold. In these patients bicarbonate infusion to keep pH above 7.10 can be justified. In all other circumstances when lactic acidosis is accompanying pulmonary oedema, cardiopulmonary arrest, grand mal seizures, biguanide therapy, ethanol ingestion, and diabetic ketoacidosis, bicarbonate therapy is not recommended.

Haemodialysis is rarely indicated as a treatment for lactic acidosis. It may be used in drug toxicity to speed up elimination of drug/toxin. It is helpful when fluid overload and cardiac or renal insufficiency is present.

Recent advances: Methylene blue, an oxidizing agent, has been used to restore cellular Nicotinamide Adinine Dinucleotide (NAD^+) with a very limited success.

Glucose, insulin infusion, nitropruside infusion, hemodialysis, peritoneal dialysis have all been used in order to treat lactic acidosis but their efficacy is unproven. Thiamine, lipoic acid and dichloroacetate have been used as they increase the activity of pyruvate dehydrogenase enzyme, which converts pyruvic acid to acetyl Co-A, but their clinical utility is not certain. Riboflavin, Coenzyme-Q, L-carnitine have also been tried.

Dichloroacetate (DCA) is an activator of pyruvate dehydrogenase. It can lower concentration of lactic acid in patients by improving the lactate utilization but when used in large clinical trial it did not show any effect on mortality. DCA, however, may be helpful in lactic acidosis in children with severe malaria.

Tris hydroxymethyl aminomethane (THAM)
It is a weak alkali and theoretical has the advantage over bicarbonate as it produces less carbon dioxide. Clinical trials do not prove THAM to be more effective than bicarbonate. The dose of THAM should be calculated by the formula (0.3 mol/L)=0.3 ×body weight in kg×HCO3 deficit.

Carbicarb is an equimolar combination of sodium carbonate and sodium bicarbonate that produces less carbon dioxide than sodium bicarbonate alone. It has theoretical advantage but trials have not demonstrated any reduction in mortality or morbidity.

Prognosis: Depends on etiology of shock/underlying disease which influences the survival but it has been shown that serum lactate levels greater than 8 mmol/L are associated with mortality rate of more than 80%.

Conclusion: Lactic acidosis is an important and frequently under diagnosed condition in critically ill patients. Timely correction of lactic acidosis can bring marked change in outcome of patients in Intensive Care Unit.

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