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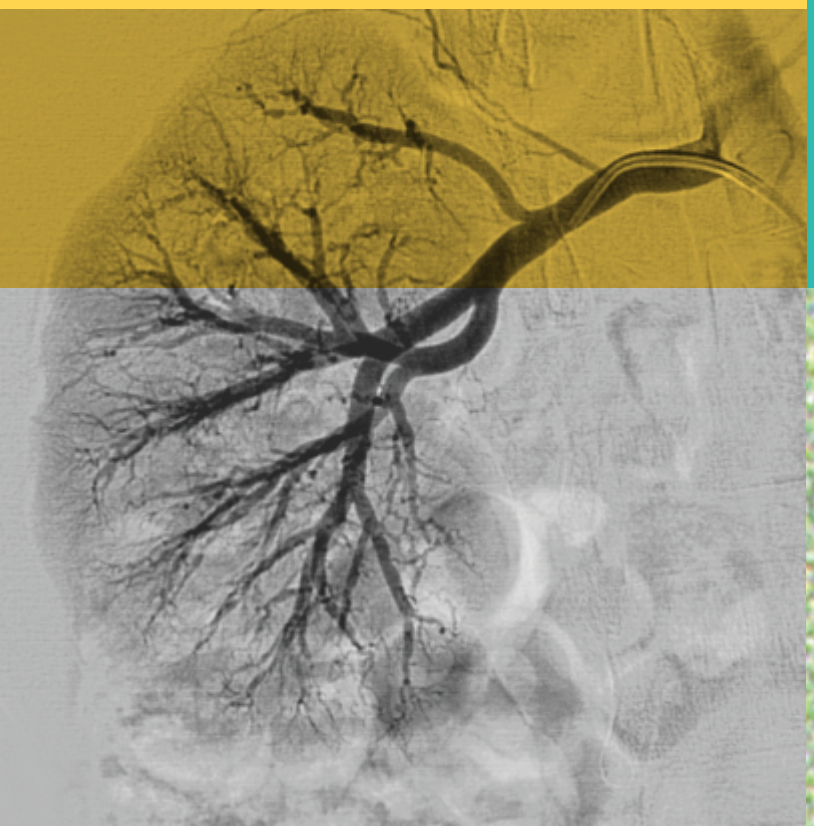

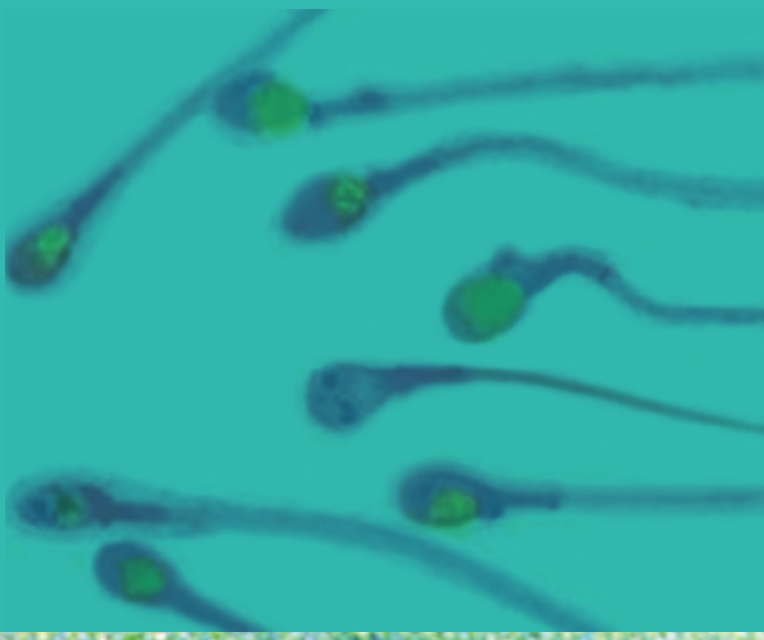

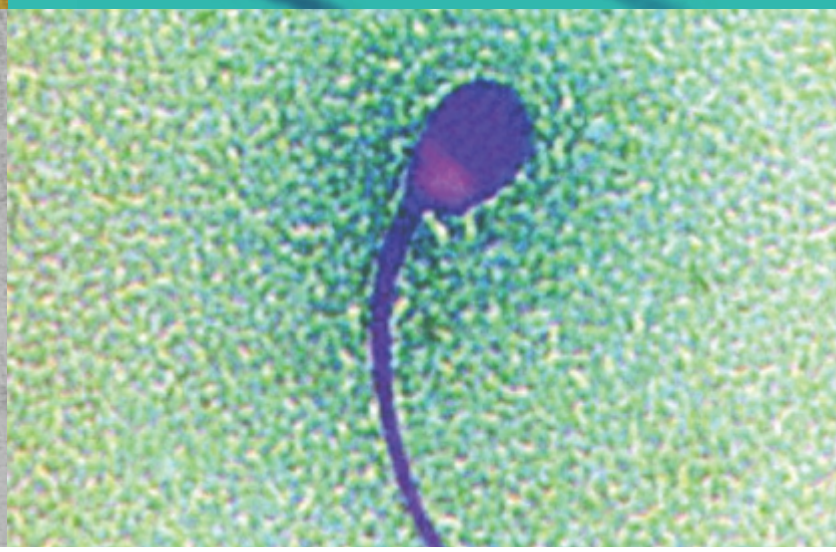

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Review Article

Myoglobinuria and Acute Kidney Injury

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Abstract

Myoglobin is a heme protein present in muscle tissues and responsible for binding and delivery of oxygen in the muscle cells for oxidative metabolism. Whenever muscle tissue is injured, that is, rhabdomyolysis occurs free myoglobin enters into circulation along with other enzymes and electrolytes and myoglobinuria occurs when the renal threshold is crossed. There are many causes of rhabdomyolysis including physical damage, infective, inflammatory, toxic, and metabolic problems. Clinically, myoglobinuria presents as muscle pain, weakness, cola colored urine, and laboratory diagnosis is done by elevated serum creatine kinase, urine dipstick positive for blood without RBC in microscopy examination. These myoglobin molecules can cause renal injury by renal vasoconstriction, proximal tubular necrosis, and distal tubular obstruction. Early anticipation of myoglobinuria and aggressive fluid resuscitation during the initial stage of injury is the mainstay of management of myoglobinuric acute kidney injury (AKI). There is lesser role of forced alkaline diuresis and mannitol than diuresis by normal crystalloid solution in myoglobinuric AKI. Renal replacement therapy should be considered in cases with life-threatening dyselectrolytemia and acidosis.

Key words: Acute kidney injury, myoglobinuria, renal replacement therapy

INTRODUCTION

Muscles account for 40% of the total body mass and whenever they are injured by any kind of assault like ischemic, toxic, infective, inflammatory or metabolic insult, there occurs dissolution of muscle fibers, that is, rhabdomyolysis resulting in release of toxic intracellular components into circulation. Rhabdomyolysis is a life-threatening clinical syndrome resulting in myoglobinuria, electrolyte disturbances, and acute kidney injury (AKI). Dissolution of myocyte membrane results in leakage of myocyte contents, including electrolytes, myoglobin, enzymes (creatine kinase [CK], aldolase, lactate dehydrogenase) into the circulatory system. Myoglobin, after entering into the circulatory system is filtered by glomerulus and causes injury to the glomerulus and tubules by various mechanisms. This renal damage is further aggravated by coexisting morbidities like hypovolemia, acidosis, infection, and ultimately patients land up in a severe and life-threatening condition that can be termed as "myorenal syndrome."

Myoglobin is a single peptide protein with molecular weight 17.8 kDa composed of 153 amino acids with single prosthetic heme group. It amounts to approximately 1-3% of dry weight of muscles and in trained athletes amount of myoglobin is higher.[1] It binds to oxygen and facilitates delivery of oxygen to sites of oxidative metabolism in muscle cells working under low oxygen tension. Myoglobin is catabolized by glomerular filtration, proximal tubular absorption by endocytosis, and proteolysis. In conditions of muscle tissue injury free myoglobin enters into circulation and most of them bind to haptoglobin and α_2 globulin. Very small amount of circulating myoglobin can be cleared by reticuloendothelial system, but when the plasma level exceeds 1.5 mg/dL, it is filtered by the kidneys.[2] Tea colored or brown colored urine occurs when the urine concentration of myoglobin exceeds 100 mg/dL.[3] Myoglobinuria is seen during conditions, where there occurs damage to the muscle fibers, that is, rhabdomyolysis. Hence, both the terms are used synonymously. During rhabdomyolysis along with release of free myoglobin into circulation there occurs electrolyte imbalance, and release of other enzymes into the circulation and hypovolemia that further aggravate

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the renal injury. Rhabdomyolysis can be due to extrinsic or intrinsic causes.

ETIOLOGY

The various causes of rhabdomyolysis can be categorized into four groups based on the mechanism of injury, that is, physical, hypoxic, chemical, and biologic. Each of the four types of injury can be initiated by either extrinsic or intrinsic factors. Overall etiology of rhabdomyolysis is described in Table 1.

Physical causes of rhabdomyolysis are overt trauma in conditions of mass disasters, road traffic accidents, assault, etc. However, rhabdomyolysis can also be precipitated by less severe injury in genetically susceptible individuals.[4] Overuse of involuntary muscles as in seizures and status asthmaticus can result in rhabdomyolysis.

Due to their peripheral location and poor vascularity, skeletal muscles are prone to ischemic injury due to external compression or internal causes. In addition to that during reperfusion free radicals are generated and they further aggravate the muscle injury.

Many drugs like statins, succinyl choline, antipsychotics, steroids, propofol, and daptomycin have been implicated as other chemicals responsible for muscle tissue injury. Risk of rhabdomyolysis increases when statins were combined with drugs those inhibit cytochrome P 450 isoenzymes. Various electrolyte abnormalities like dysnatremia, hypokalemia, hyperphosphatemia can cause rhabdomyolysis and myoglobinuria.

Table 1: Causes of rhabdomyolysis

Mechanism of injury	Type of injury
Physical injury	Extrinsic factors-crush injury, trauma, heat stroke, electrocution, burns, hypothermia, march hemoglobinuria
	Intrinsic factors-seizures, severe agitation, malignant hyperthermia, neuroleptic malignant syndrome, status asthmaticus
Hypoxic injury	Extrinsic-carbon monoxide poisoning, cyanide poisoning
	Intrinsic-compartment syndrome, ischemia-reperfusion injury, immobilization, vascular thrombosis, sickle cell trait, vasculitis
Chemical injury	Extrinsic-alcohol, steroids, neuromuscular blocking agents, lipid lowering agents, drug abuse, organic solvents
	Intrinsic-hypokalemia, hypophosphatemia, hypocalcemia, hyponatremia, hypernatremia
Biologic injury	Extrinsic-bacterial, viral, parasitic myositis, snake bite, insect bite
	Intrinsic-dermatomyositis, polymyositis, adrenal insufficiency, hypothyroidism, hyperaldosteronism, diabetic ketoacidosis, hyperosmolar states
	Genetic disorders of carbohydrate metabolism (McArdle's disease, Phosphofructokinase deficiency, α-glucosidase deficiency, phosphohexose isomerase deficiency)
	Lipid metabolism (carnitine deficiency, carnitine palmitoyltransferase deficiency)
	Muscular dystrophy

Among infectious agents bacterial, viral and parasitic causes are important. Legionella infection is the most common bacterial cause of rhabdomyolysis.[5] Gram positive infection by Streptococcus pyogenes, *Staphylococcus aureus* are also important cause of pyomyositis. Influenza A and B infection is the most common viral culprit for myositis. Cases of rhabdomyolysis after HIV, EBV, and Coxsackie virus infection have also been reported. In addition cases of rhabdomyolysis after infection with candida, aspergillus, and malaria have been reported. Apart from infections snake bite, scorpion stings are important and most frequently encountered causes of rhabdomyolysis and myoglobinuria.

Some inborn errors of carbohydrate and lipid metabolism have also been implicated in rhabdomyolysis and myoglobinuria. Mc-Ardle's disease is the most frequent underlying cause. Autoimmune disorders such as polymyositis, dermatomyositis, and hereditary forms of muscular dystrophy can also cause rhabdomyolysis. Endocrinal causes like hypothyroidism, hypoadrenalism, diabetic ketoacidosis can also present with myoglobinuria.

Pathophysiology

The entity rhabdomyolysis associated acute renal failure (ARF) was well known from World War I. However, the underlying pathophysiology was first explained by an experimental model of Bywaters and Stead.[6] Three basic mechanisms underlie myoglobin induced nephrotoxicity:

1. Renal vasoconstriction.
2. Direct heme protein induced cytotoxicity.
3. Intraluminal cast formation and tubular obstruction.

Renal vasoconstriction

Renal vasoconstriction is a characteristic feature of myoglobinuric AKI and it can be explained by several mechanisms. First, severe muscle necrosis in crush injuries cause fluid accumulation in third space and resultant intravascular fluid (IVF) depletion[7] and aggressive volume repletion during early postinjury period dramatically decreases kidney injury. This IV hypovolemia results in activation of renin-angiotensin system, vasopressin and sympathetic nervous system and further aggravates vasoconstriction. Second, severe muscle injury generates endotoxins like endothelin-1, thromboxane A2, TNF-α and they activate endotoxin cytokine cascade resulting in renal vasoconstriction.[8,9]

Third, nitric oxide (NO), a potent endogenous vasodilator is scavenged by the heme proteins myoglobin.[10,11] In the setting of myoglobinemia, renal hypoperfusion is exacerbated because myoglobin maintains mean arterial pressure during volume depletion states by NO scavenging and increasing peripheral vascular resistance. Thus, hypovolemia could not be detected clinically and ischemic tissue injury is aggravated.

Moreover, renal vasoconstriction can facilitate heme toxicity by decreasing GFR and prolonging their circulating half-life, promoting proximal tubular uptake and increasing the propensity for cast formation. IV volume depletion stimulates fluid reabsorption in tubules and increases intraluminal myoglobin concentration, favors cast deposition, and tubular obstruction.

Myoglobin mediated proximal tubular cytotoxicity

Heme proteins and myoglobin have a direct cytotoxic effect on the proximal tubules. Heme proteins can exacerbate ischemic renal injury by intensifying renal vasoconstriction in the setting of volume depletion.[12] They decrease ATP availability via nonhemodynamic iron-mediated mechanism.[13] Heme protein endocytosis by the proximal tubular cells directly sensitizes the plasma membrane to phospholipase A2 mediated injury in ischemia-reperfusion.[14]

Myoglobin contains iron as ferrous oxide (Fe^{2+}) necessary for binding with oxygen. However oxidation of ferrous to ferric oxide generates hydroxyl radical that can injure tubular epithelium. This fact is further strengthened by the experiments where iron chelators (deferoxamine) and antioxidants like glutathione have shown protective effect in myoglobinuria induced tubular damage.[15,16] Myoglobin itself can exhibit peroxidase like enzyme activity and leads to uncontrolled oxidation of biomolecules, lipid peroxidation, and generation of isoprostanes.[17]

Intraluminal cast formation and tubular obstruction

Heme protein cast formation and tubular obstruction primarily occurs in the distal tubules. Acidic urine, high concentration of myoglobin, and presence of Tamm-Horsfall protein largely determine formation of tubular casts. More the intraluminal concentration of myoglobin, higher is the chance of cast formation. Second most important factor is acidic urine. In acidic pH solubility of myoglobin is decreased and it forms aggregate with Tamm-Horsfall proteins.[18] Since, Tamm-Horsfall proteins are primarily synthesized in distal tubules and stasis of myoglobin occurs more in distal tubules, they become the primary location for cast formation and resultant tubular obstruction.

Additional mechanisms of myoglobinuric acute renal injury are:

1. Hyperphosphatemia potentiating ischemic and nephrotoxic renal damage.
2. Hyperuricemia contributes to cast formation and distal tubule obstruction.
3. Severe crush injury and rhabdomyolysis triggers disseminated IV coagulation and results in intrarenal micro thrombus formation and aggravation of ischemic damage.

Hence, AKI in myoglobinuria is multifactorial and therapeutic approaches for prevention and treatment of rhabdomyolysis-induced acute kidney injuries are usually based on these proposed mechanisms.

CLINICAL PRESENTATION

Clinical presentation of rhabdomyolysis is widely variable depending upon its variable underlying etiology. The classic triad of symptoms of rhabdomyolysis includes muscle pain, weakness, and dark brown colored urine. Most frequently involved muscle groups are calves, thigh and lower back muscles. In conditions of severe injury perfusion may be compromised and pressure necrosis on the overlying skin may be seen. Nonspecific symptoms include fever, generalized myalgia, nausea, vomiting, tachycardia, etc. Patients can have rhabdomyolysis in absence of dark urine. Color of urine can vary from light pink tinge to tea colored, cola colored to dark black.[19] Early complications of rhabdomyolysis include hyperkalemia, hypocalcemia, and cardiac arrhythmia due to dyselectrolytemia. Liver dysfunction is seen in 25% patients with rhabdomyolysis.[20] ARF and disseminated IV coagulation usually develops 12-72 h after acute insult.[21]

LABORATORY INVESTIGATIONS

A thorough history and physical examination can provide clue to the underlying cause of rhabdomyolysis and myoglobinuria. CK levels are the most sensitive and specific indicators of myocyte injury. Elevated serum CK level at least 5 times the normal value with predominance of CK-MM fraction denotes striated muscle injury. Level of CK rises within 12 h of muscle injury, peaks in 1-3 days and declines 3-5 days after cessation of injury. Higher CK levels correlate with greater muscle injury. However, prediction of mortality and development of AKI from CK values is less reliable.[22] When patient is on serial CK monitoring if the levels increase or fails to normalize despite therapy, it may suggest ongoing muscle injury or progression to ARF.

Estimation of serum and urine myoglobin is less reliable in the diagnosis of rhabdomyolysis and myoglobinuria and hence should not be done routinely. During the early phase of muscle injury, its serum level is elevated. Myoglobin has a short half-life of 2-3 h and it is rapidly cleared by metabolism to bilirubin and renal excretion. Serum level of myoglobin also comes to normal after 6-8 h of muscle injury. Urine myoglobin is neither a sensitive test for rhabdomyolysis nor specific for the development of AKI. Hence, its routine testing should be discouraged.

Apart from CK other enzymes elevated in rhabdomyolysis are carbonic anhydrase III in skeletal muscles, aldolase, troponin I, troponin T, lactate dehydrogenase, aminotransferases, etc.

Creatinine is elevated to a greater extent than blood urea nitrogen in cases of rhabdomyolysis with ARF. Electrolyte abnormalities encountered are hyperkalemia, hyperphosphatemia due to release from the intracellular compartment. Serum calcium levels initially decrease as due to influx into the intracellular compartment and later on hypercalcemia occurs.

Biochemical investigations to find out the cause of rhabdomyolysis should be done if no specific cause identified from history and physical examination. Patients should be monitored for the development of disseminated IV coagulation.

MANAGEMENT

Acute kidney injury associated with myoglobinuria is the most serious complication encountered in cases of rhabdomyolysis. Incidence of AKI in myoglobinuria is reported from 13% to 50% due to the use of different definition of AKI and different clinical circumstances.[8,23] A study by Melli *et al*. in 475 hospitalized patients with rhabdomyolysis found out the incidence of AKI was as high as 46%.[24] Rhabdomyolysis resulting in ARF accounts for 3-15% of all cases of ARF.[24,25] Mortality from rhabdomyolysis and myoglobinuria is variable due to different underlying etiologies and coexisting conditions. Among patients treated in intensive care units mortality has been reported to be 59% if associated with AKI and 22% when there were no features of AKI.[22]

The treatment of rhabdomyolysis comprises resuscitation and initial stabilization of the patient along with aggressive fluid therapy. Early hydration is the key to prevent or decrease the severity of AKI in patients with rhabdomyolysis.[26] IVF should be started from prehospital care and maintained with continuous monitoring of vital parameters and urine output. Retrospective studies have found the incidence of AKI was lower when IVF initiated in crush injury patients immediately than those patients where IVF could not be administered early.[7,27] Forced diuresis when started within 6 h of injury minimizes the risk of AKI.

Many experimental studies suggest the benefits of mannitol in cases of rhabdomyolysis. Mannitol, an osmotic diuretic prevents intratubular pigment deposition and cast formation. It acts as a vasodilator and free radical scavenger, thus minimizing renal injury in rhabdomyolysis. However, there is little clinical evidence to support its use. Moreover, if mannitol is administered immediately after renal insult without adequate fluid resuscitation, the resulting vasodilatation can decrease renal cortical ATP and further worsen the renal injury.[25]

Alkalization of urine by sodium bicarbonate has been postulated to reduce renal damage by preventing tubular cast formation. This therapy is controversial as a large volume of only crystalloid administered can alkalinize the urine sufficiently to prevent cast formation.[28,29] Moreover, large doses of bicarbonate can exacerbate hypocalcemia when hypovolemia is corrected.

There is little clinical evidence supporting the use of "mannitol-bicarbonate cocktail infusion" in myoglobinuria with AKI. Homsi *et al*. have demonstrated that volume expansion with saline alone can prevent further progression to renal failure.[30] A retrospective review of case records by Brown *et al*. have also found that there was no difference in incidence of ARF, requirement of dialysis, and mortality rate among patients who received mannitol and bicarbonate than those who did not receive.[31]

Antioxidants and free radical scavengers have a theoretical role in ischemia-reperfusion injury seen in rhabdomyolysis. Pentoxiphylline improves microvascular circulation and also decreases neutrophil adhesion and cytokine release. Other antioxidant molecules those may have role are Vitamin E, Vitamin C, 21-aminosteroid, etc.

Renal replacement therapy

Despite optimal treatment 10-50% patients with myoglobinuria develop AKI requiring renal replacement therapy.[23] Severe acidosis and hyperkalemia necessitates immediate dialysis. Daily hemodialysis or continuous hemofiltration is required to remove the urea and potassium released form muscle injury. Peritoneal dialysis is ineffective in myoglobinuria. Frequent intermittent hemodialysis may be required for rebound hyperkalemia and acidosis and moreover hemodialysis may be ineffective in removing circulating myoglobin. Continuous renal replacement therapy (CRRT) modes like continuous veno-venous hemofiltration and continuous veno-venous hemodiafiltration have the advantage of aborting these rebound complications and in addition to that convection removes

myoglobin better than diffusion process. CRRT using high-flux filters are more effective in removing high molecular weight proteins like myoglobin. However, it is not clear that removal of myoglobin prevents or alters the clinical course of AKI. Hence, prophylactic CRRT is not recommended for myoglobin removal.

CONCLUSION

Rhabdomyolysis and the resultant myoglobinuria is a potentially life-threatening condition encountered in conditions of extrinsic or intrinsic muscle injury. Whenever faced with such clinical scenario, aggressive fluid resuscitation should be done. Patients should be monitored by serum CK level and physicians should be watchful for the development of acute and delayed complications. Electrolyte imbalances should be treated as per protocol. There is no role of mannitol and forced alkaline diuresis in the management of myoglobinuria. Renal replacement therapy should be started in conditions of hyperkalemia and acidosis. CRRT is preferred over intermittent hemodialysis in managing patients with myoglobinuric acute kidney injuries.

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