Update in
Anaesthesia

Rhabdomyolysis

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Summary

Rhabdomyolysis describes muscle breakdown due to a number of different pathological processes. This article describes the aetiology, clinical recognition and treatment of the condition.

INTRODUCTION

Rhabdomyolysis is the breakdown of striated muscle. There are many causes that all ultimately progress to myocyte necrosis and release of intracellular contents into the circulation. This can produce life threatening complications including hyperkalaemia and acute kidney injury (AKI).

EPIDEMIOLOGY

In the ICU setting, the most common causes of rhabdomyolysis are muscular trauma and vascular obstruction.[1] Rhabdomyolysis occurs in up to 85% of patients with traumatic injuries.[2] Alcohol has been implicated in the development of rhabdomyolysis in up to 20% of cases.[3] About a third of all patients with rhabdomyolysis will develop AKI and it is suggested that 5-25% of all AKI results from rhabdomyolysis. Patients with severe injuries that develop rhabdomyolysis induced AKI have a mortality of approximately 20%, but this is higher if multiple organ dysfunction is present.[4]

PATHOPHYSIOLOGY

Muscle necrosis is the end-point of rhabdomyolysis. It results from either direct sarcolemmic injury (the sarcolemma is the calcium storage system within cells), or hypoxia, causing ATP depletion and sodium-potassium pump failure. This leads to sodium influx and accumulation of free cytosolic ionized calcium, as the cell attempts to restore electrochemical neutrality via the sodium-calcium exchange mechanism.

High intracellular calcium activates calcium-dependent proteases and phospholipases, causing toxic metabolite production and cell death. Potassium, phosphate, myoglobin, creatine kinase (CK), creatinine and nucleosides (which are metabolised to urate) leak into the circulation. The subsequent inflammation and oedema leads to fluid accumulation in affected muscles and intravascular volume depletion.

AETIOLOGY

Causes of rhabdomyolysis can be classified into traumatic and non-traumatic (Table 1). The most common cause is direct trauma to the muscle, either from being crushed or from direct pressure, for example a patient lying on the floor for a long period, unable to get up.

Table 1. *Causes of rhabdomyolysis.*

Traumatic	Non-traumatic
• Crush injury	• Ischaemic insult
• Entrapment	• Substance misuse - alcohol, cocaine, amphetamines, ecstasy
• Prolonged immobilisation	• Drugs - statins, fibrates, antipsychotics, antidepressants
• Electrical injury	• Toxins - carbon monoxide, heavy metals, snake venom
• Excessive muscle activity - marathon running, status epilepticus, malignant hyperpyrexia	• Infection - tetanus, Legionella, viral, sepsis syndrome
• Heat-related - heat stroke, neuroleptic malignant syndrome (NMS), hypothermia (rarely)	• Electrolyte disturbance - hypokalaemia, hypo/hypernatraemia, hypocalcaemia, hyerphosphataemia, hyperosmolar non-ketotic coma, diabetic ketoacidosis, hypo/hyperthyroidism

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PRESENTATION

Clinical manifestations

The clinical presentation of rhabdomyolysis varies, depending on the aetiology and severity. It may range from an asymptomatic rise in serum CK to hypovolaemic shock with life threatening arrhythmias. Muscle pains and weakness are common and often associated with general malaise, nausea, tachycardia and confusion. Dark coloured urine may be the first indication of muscle damage.

The 'classic' triad of symptoms includes muscle pains, weakness and dark urine, but is seen in less than 10% of patients.[4]

Laboratory features

Biochemical markers confirm the diagnosis and can be used to predict prognosis. Serum CK levels are the most sensitive indicator of muscle damage, rising within the first twelve hours of injury, peaking at one to three days and declining at three to five days.[4] A serum CK level over $5000U.L^{-1}$ is associated with an incidence of AKI of over 50%.[4] Levels are directly proportional to the extent of muscle injury. Compartment syndrome, compounding the injury, may further increase serum CK.[5]

Myoglobin is one of the significant compounds released after muscle disintegration. High circulating levels produce dark-brown discolouration of the urine, as myoglobin is filtered in the kidney. Haematuria and myoglobinuria often co-exist, particularly in the context of trauma. The absence of myoglobinuria does not exclude the diagnosis of rhabdomyolysis so clinical use is questionable.

Many metabolic derangements occur due to the rapid influx of calcium into cells. These include hyperkalaemia, hyperuricaemia, hyperphosphataemia, hypermagnesaemia and initially hypocalcaemia, as calcium concentrates in myocytes. Hyperkalaemia is an early feature; electrolytes should be measured as soon as the diagnosis is made. High anion gap metabolic acidosis may develop in severe rhabdomyolysis due to lactic acid production in ischaemic muscles.

COMPLICATIONS

Early

Severe hyperkalaemia may lead to arrhythmias and cardiac arrest, especially in association with profound hypovolaemia, hypocalcaemia and acidosis.

Early or late

Compartment syndrome may develop and is exacerbated by the presence of hypotension. Compartment pressures greater than 30mmHg are likely to cause significant muscle ischaemia and subsequent secondary rhabdomyolysis. Hepatic dysfunction occurs in approximately 25% of individuals.[6]

Late

Disseminated intravascular coagulation may occur up to 72 hours following the initial insult. Acute kidney injury is the most serious complication.[7] The mechanism is not completely understood, but it is thought to be due to a combination of renal vasoconstriction, hypovolaemia, mechanical obstruction by intraluminal cast formation and direct cytotoxicity.

During the recovery phase, hypercalcaemia may result from accumulation in muscle and from iatrogenic administration of calcium supplementation during periods of hypocalcaemia.[8]

MANAGEMENT

Early recognition and initiation of treatment is key to the stabilisation of life threatening electrolyte disturbance and metabolic acidosis. Prompt aggressive fluid resuscitation with crystalloid is paramount and is the single most important factor in reducing the incidence of AKI. Alkalinisation of the urine with crystalloid resuscitation is considered standard. The use of bicarbonate and mannitol therapy has been used, however observational data suggest that they provide no additional clinical benefit to volume expansion with crystalloid (see below).

Initial resuscitation

As soon as the diagnosis is confirmed, intravenous access should be established and baseline measurements, including electrolytes and an arterial blood gas sample, taken. Acute hyperkalaemia should be treated with standard therapy including insulin, glucose and bicarbonate. As much as 10 litres of fluid may be sequestrated into injured muscle. Intravenous crystalloid therapy with sodium chloride 0.9% should be started immediately. Fluid should be titrated to achieve a urine output of 200- $300ml.h^{-1}$. There is no good evidence to show that alkaline diuresis is superior to sodium chloride 0.9%.[9] The administration of both sodium chloride (0.9%) and isotonic sodium bicarbonate (1.26%) is an acceptable approach, that can be used to avoid a worsening hyperchloraemic metabolic acidosis. Resuscitation should ideally be guided by the use of invasive monitoring.

Intravenous mannitol can also be used, as it promotes renal blood flow and diuresis, although there is no evidence that this therapy leads to beneficial outcomes.

Rationale for bicarbonate and mannitol therapy

Alkalinisation of the urine is achieved by using 1.26% sodium bicarbonate of up to $500ml.h^{-1}$, aiming for a urinary pH of greater than 6.5. This potentially prevents precipitation and degradation of myoglobin in the urinary tubules. It is also useful in the management of hyperkalaemia and acidosis, however neither therapy has been subject to randomised clinical trials. Observational data suggest that the addition of mannitol and bicarbonate have no effect on the development of acute kidney injury, need for dialysis or death. If sodium bicarbonate is used, serum bicarbonate, calcium and potassium should be closely monitored.[10]

Compartment syndrome

Irreversible muscle and nerve damage can occur if there is a delay in the recognition and management of compartment syndrome. Neurovascular compromise implicates the need for fasciotomy. Intracompartmental pressures consistently greater than 30mmHg, despite reductive measures, indicate a clear requirement for fasciotomy.

Renal replacement therapy

Established acute kidney injury, or the presence of refractory hyperkalaemia and acidosis, may necessitate renal replacement therapy (RRT). It is unusual for fluid overload to be an indication for RRT

in rhabdomyolysis. Haemodialysis corrects metabolic and electrolyte disturbances rapidly and efficiently. The prognosis of AKI secondary to rhabdomyolysis is good, with renal function usually returning to normal within 3 months.[10]

SUMMARY

Rhabdomyolysis is often encountered in the intensive care setting. Patients may have few symptoms so a high level of suspicion should be maintained. Serum CK is the most sensitive indicator of muscle injury.

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