Rhabdomyolysis.
The role of diagnostic and prognostic factors

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Summary

Rhabdomyolysis, literally meaning the breakdown of muscle tissue, is a common syndrome with many causes, acquired ones such as exertion, trauma, infections, temperature extremes, drugs, toxins, electrolyte and endocrine abnormalities, and congenital ones such as myopathies and connective tissue disorders. All results in a common pathophysiologic pathway which ends with the dispersing of muscle tissue content into the circulation. Rhabdomyolysis has characteristic clinical, laboratory and radiologic features, but does require a high index of suspicion so that the diagnosis would not be missed. The sensitivity and specificity of the various characteristics, as well as clinical guidelines, are discussed in this paper. The syndrome may present with several complications, e.g. arrhythmias, electrolyte abnormalities, acute renal injury, acidosis, volume depletion, compartment syndrome and disseminated intravascular coagulation. The prognosis is highly variable and depends on the underlying etiologies and complications, but is in general considered as good. The milestone of treatment is vigorous fluid resuscitation. Treatment options, in practice and in research, are discussed in the following pages.

KEY WORDS: rhabdomyolysis.

Introduction

Rhabdomyolysis is a syndrome characterized by breakdown of muscle tissue, followed by dispersing its intracellular components into the circulatory system. These components include electrolytes, purines, enzymes (such as creatine kinase) and myoglobin. This syndrome is associated with many diseases, drugs, medications, toxins and injuries. The syndrome may be expressed as elevated levels of blood creatine phosphokinase (CK) and leading to acute kidney injury and death. Rhabdomyolysis was first reported in Germany in 1881, but the syndrome was characterized in detail by Bywaters and Beall during the Battle of London in the 2nd World War. It is suggested that during the exodus from ancient Egypt, the bible describes a "plague" characterized as similar to rhabdomyolysis among the people of Israel, due to quail consumption, thus intoxication of hemlock herbs consumed by the quail 1.

Pathophysiology

There are many causes for rhabdomyolysis, but they seem to lead to a final common feature, which is the breakdown of muscle tissue, destruction of the myocyte and distribution of its components into the circulatory system. In the normal myocyte, a low level of Calcium is maintained by a Ca2+ ATPase pump (concentrating intracellular Calcium in the sarcoplasmic reticulum and mitochondria), and a Na/Ca exchanger ion channel, powered by Sodium influx, due to the gradient created by the Na/K ATPase pump. All these mechanisms depend, directly or indirectly on ATP as a source of energy. The lack of ATP causes the cell's homeostasis to collapse, causing the intracellular level of Calcium to rise. In turn, the rise of Calcium level activates intracellular proteolytic enzymes, thereby degrading the myocyte. As the cell breaks down, large quantities of Potassium, aldolase, phosphate, myoglobin, CK, lactate dehydrogenase (LDH), aspartate transferase (AST) and urate leak into the circulation 2. When more than 100g of muscle tissue is degraded the plasma's myoglobin binding capacity is overwhelmed and free myoglobin causes renal morbidity by several mechanisms 3-5.

Causes

There is a large variety of causes for rhabdomyolysis, all leading to muscle ischemia and cell breakdown. The most common among adult populations are muscle exertion illicit drugs, alcohol abuse, medications, muscle diseases, trauma, Neuroleptic Malignant Syndrome (NMS), seizures and immobility 6. Among pedi-
Excessive heat caused by heat stroke 33,34, malignant being damaged 38. The higher the heat a body will ab-

tion of hyperaldesteronism or pseudoaldestero-

duced rhabdomyolysis was reported as a complica-

tion 26,27, Addison’s disease 28, hypothyroidism 29, hy-

Electrolyte and endocrine abnormalities
Severe electrolyte abnormalities disrupt the cell’s membrane homeostasis, mainly by disturbing the Na/K ATPase pump. Hyponatremia 17, hypernatremia 18, hypokalemia 19 and hypophosphatemia (usually as part of diabetic ketoacidosis 20) may result in rhabdomyolysis. It has been suggested that extreme exercise with intense fluid consumption by athletes may cause hyponatremia induced rhabdomyolysis 21. Poly-

dypisia alone can initiate dilutional hyponatremia fol-

Factors increasing the risk of exertional rhabdomyo-

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Muscle ischemia
Muscle ischemia means deprivation of oxygen from muscle tissue, resulting in decreased levels of ATP production. Prolonged ischemia may lead to muscle cells necrosis. Ischemia may be caused by a general condition, such as shock, hypotension, CO intoxication 43 and sickle cell trait 15. Alternatively, it may be a result of a localized specific cause, such as blood vessel thrombosis, embolism, compartment syn-

drome 44, or compression of a vessel (e.g. surgical tourniquets 45, tight dressings or casts and vessel clamping 46,47). Prolonged immobilization, mainly due to substance or alcohol abuse, coma or anesthasia, is a major cause of compression of blood vessels. Like trauma, pathophysiology actually takes place once pressure is relieved from the damaged tissue, and the necrotic muscles release their components into circulation 48. Known positions resulting in rhab-

domyolysis are lateral decubitus, lithotomy, sitting, knee-to-crotch, prone position 49 and harness hang-

Temperature extremes
Excessive heat caused by heat stroke 33,34, malignant hyperthermia syndrome 35 and neuroleptic malignant syndrome 36,37 may result in muscle damage, on the cellular level. A body core temperature of 42°C (107.6°F) for 45 minutes to 8 hours was established to be the thermal maximum, meaning the level and duration of heat that muscle cells can endure without being damaged 38. The higher the heat a body will absorb, cellular destruction will occur at a higher and faster extent 39. Malignant hyperthermia is a condition usually ascribed as a genetic susceptibility to anesthetic drugs, causing hyperthermia, increased metabolic rate, elevated respiratory rate, pulse, rigidity and rhabdomyolysis. It may also be triggered by exer-
cise (exercise induced malignant hyperpyrexia) 40. In neuroleptic malignant syndrome, the mechanism sug-
gested is that neuroleptic medications induce abnor-
mal calcium availability in muscle cells of susceptible individuals and trigger muscle rigidity, rhabdomyolysis and hyperthermia 37.

Drugs
Rhabdomyolysis may result from substance abuse, pre-
scription and nonprescription medications. Substances that are commonly abused include ethanol, methanol and ethylene glycol 52,53, heroin, methadone 54, tobacco, cocaine, amphetamine, 3,4-methylenedioxymetham-
phetamine (MDMA, ecstasy), phencyclidine 55, lysergic acid diethylamide (LSD) 56, benzodiazepines 57, barbiturates 58 and toluene (from glue sniffing) 59.

Alcohol can induce rhabdomyolysis through a combi-
nation of mechanisms including immobilization with muscle compression (due to immobilization), direct myotoxicity (due to inhibition of calcium accumulation by the sarcoplasmic reticulum and alteration of membrane viscosity with derangement of membrane ion transporters), aberration in myocyte carbohydrate metabolism, dehydration and electrolyte abnor-

ties (hypokalemia and hypophosphatemia) 55,60. Co-

caine induced rhabdomyolysis is caused by either va-
sospasm with muscular ischemia, hyperpyrexia, seizures, coma with muscle compression or direct myofibrillar damage 55. Drug and alcohol abusers are
often malnourished, with resultant diminished glyco-
gen storage and ATP reserve.

Excessive use of barbiturates, benzodiazepines and
other sedative and hypnotic drugs causes depression of
the central nervous system with prolonged immobi-
ization and muscle compression, resulting in hypox-
ia, suffering and destruction.[95, 96]

Rhabdomyolysis may also result from both prescribed
and over-the-counter medications including salicy-
lates,[61] statins (e.g., simvastatin, lovastatin, pravas-
tatin, rosuvastatin, cerivastatin)[62-65], especially sim-
vastatin, statin-fibrate combination,[66] theophylline,[67]
cyclic antidepressants, selective serotonin reuptake
inhibitors,[68, 69] phenylpropanolamine containing diet
pills,[70] fibrin acid derivatives (e.g., bezafibrate, clofi-
brate, fenofibrate, gemfibrozil)[71, 72], neuroleptics,[73]
anesthetic (e.g. propofol)[74] and paralytic agents (the
malignant hyperthermia syndrome)[75], quinine,[76] ana-
abolic steroids,[77, 78] corticosteroids.[79] Several mecha-
nisms were related to statin induced rhabdomyolysis.

Since cholesterol is an important building block of
the cell's membrane, and its synthesis is blocked, the
result is also unstable skeletal muscle cell membrane.
In addition, mitochondrial respiratory function is inter-
rupted due to coenzyme Q10 deficiency. A third mecha-
nism is the presence of abnormal prenylated proteins which causes an imbalance in intracellular
signal transduction.[80]

Toxins

Toxin induced rhabdomyolysis include carbon monox-
ide (CO)[83], snake bites,[81] spider venom,[82] massive
honey bee and wasps envomination,[83, 84] and quail
eating (it nourishes from hemlock herbs).[1] CO gas
has a higher affinity to hemoglobin than oxygen, thus
combining with it to form carboxyhemoglobin in the
blood, preventing the binding of oxygen, causing
muscle hypoxia and rhabdomyolysis.

Trauma

Rhabdomyolysis may occur due to traumatic events,
such as blunt trauma, crush injury, electrical injury or
third degree burns.

Blunt trauma may be due to direct blow or motor-ve-
icle crush (including acceleration-deceleration
mechanism). Crush injuries are associated with mass
incidents and severe trauma, such as terror at-
tacks, bombing, earthquakes and building collapses,
train accidents and mining accidents. For instance,
earthquakes result in 3% to 20% of crush injuries, of
which 74% involve the lower extremity.[85] The
rhabdomyolysis pathophysiology actually takes place
once pressure is relieved from the damaged tissue,
and the necrotic muscles release their components into circulation,[46] for example, once people are ex-
tracted from a crushed vehicle. High voltage electrical
injury, caused by lightning strike or high voltage pow-
er supply, or extensive third degree burns results in
rhabdomyolysis due to direct myofibrillar damage.[86]
However, extensive thermal third degree burns could
also result in rhabdomyolysis. Regardless of the ini-
tial cause, late onset Rhabdomyolysis could occur
due to immobilization or circumferential burns con-
tracts. The treatment of burn induced rhabdomyol-
ysis presents a great challenge because burn treat-
ment itself requires vigorous fluid overload, thus mak-
ing it difficult to add more fluids for rhabdomyolysis management.[86]

Infections

Several mechanisms are ascribed to infection in-
duced rhabdomyolysis: bacterial invasion of a mus-
cle, low energy related enzymatic activity, tissue hy-
poxia (due to sepsis, general hypoxia, acidosis, dehy-
dration and electrolyte disturbances)[87], high lysoso-
mal enzymatic activity[88] and endotoxins.[89]

Numerous bacterial, viral, fungal and protozoal in-
fecions can lead to rhabdomyolysis. Viral infections as a
cause of rhabdomyolysis have been described in
many reports worldwide, of which influenza types A
(including recent reports of H1N1 subtype)[90, 91] and B
are the most common.[92] Other viral infections induc-
ing rhabdomyolysis include HIV, Coxsackievirus, Ep-
stein-Barr virus, Echovirus, Cytomegalovirus, Aden-
virus, Herpes simplex virus, Parainfluenza, Varicel-
la-Zoster virus[92] and West Nile virus.[93] Bacterial in-
fecions are often associated with rhabdomyolysis in
adults, most commonly Legionella. Other species de-
scribed as associated with rhabdomyolysis are Strept-
ococcus pneumoniae, Staphylococcus aureus, Streptococcus viridans, Salmonella species, Staph-
lococcus epidermidis, Francisella tularensis, Strepto-
coccus faecalis, Meningococci, Hemophilus influen-
zae, E.coli, Pseudomonas aeruginosa, Klebsiella, Enterococcus faecalis, Bacteroides, B streptococcus, Strept-
coccus pyogenes, Listeria species, Vibrio species,
Leptospirosis species,[95] Brucella species, Bacillus species and Clostridium species.[92]

Clinical Presentation

Because of the many possible causes, there is a variety of rhabdomyolysis’ presentations. It may be severe when substantial muscle damage has occurred, or, vice versa, subclinical, when the damage is minor. A classic triad was described inclusive of muscle aches, weakness and dark, tea colored urine. Especially when accompanied by clues of muscle damage, this should raise the suspicion of Rhabdomyolysis. This is especially true in pediatrics. Some more specific symptoms include muscle tenderness, swelling, cramping, stiffness, weakness and loss of function of the relevant muscles. The most common muscle groups involved are postural muscles, such as lower back, thighs and calves. Muscle swelling may not be apparent until after intravenous (IV) fluids rehydration. Other symptoms may be of non specific nature, such as fever, malaise, abdominal pain, nausea and vomiting. Change of mental status may occur due to the underlying cause (e.g., trauma, toxins or drugs, infections, electrolyte abnormality, or urea induced encephalopathy).

Physical examination might reveal limb induration or skin changes due to ischemic damage of involved tissues (e.g. blisters, discoloration). However, there may be no signs of muscle involvement. Rhabdomyolysis could be an incidental finding of a laboratory test. Anyhow, purposeful efforts should be made to identify an underlying cause.

Work-Up

A high index of suspicion is crucial for diagnosing rhabdomyolysis, since classic presentation such as muscular swelling, pain and tenderness may not be eminent, or even be absent. A thorough history must be taken. The definitive diagnosis is made by laboratory tests including serum CK and urine myoglobin. A skeletal muscle biopsy can be used to establish the diagnosis, but is not obligatory.

Serum CK (Creatine Kinase)

Serum CK concentration, mainly the CK-MM subtype, is the most sensitive indicator of damage to muscles. Serum CK begins to rise approximately 2 to 12 hours after the onset of muscle injury, peaks within 24 to 72 hours, and then declines gradually in 7-10 days. A persistently elevated CK level suggests continuing muscle injury, development of a compartment syndrome or continuing muscle stress (e.g. prolonged exercise or infection). Currently, there is not a clearly agreed level of serum CK that is evident for diagnosis of rhabdomyolysis. However, a CK level higher than 5 times of its normal value is accepted by many authors as diagnostic criteria. Moreover, some studies establish the low specificity of serum CK levels. Kenney et al. found in their contingent of 499 young healthy recruits a CK elevation of 10 times regarded as normal, none diagnosed as exertional rhabdomyolysis, and suggesting either coexisting myoglobinuria or CK level of 50 folds of normal as a diagnostic threshold. Statin induced rhabdomyolysis is commonly defined with marked CK elevation greater than 10 times the upper limit of normality, with muscle symptoms and usually with brown urine with myoglobinuria.

Serum and urine myoglobin

Myoglobin is normally bound to plasma globulins, and is maintained at a low serum level of 0 to 0.003mg/dL.
Once circulating myoglobin levels have exceeded 0.5 to 1.5mg/dL it overwhelms its protein binding capacity, tubule endocytosis rate and metabolism rate, and is rapidly excreted in the urine\textsuperscript{107}. Note that myoglobinuria is pathognomonic to rhabdomyolysis, but is not necessarily visible. Elevated serum myoglobin and myoglobinuria are reliable indicators for rhabdomyolysis, but present some limitations. Serum myoglobin levels rise and drop much faster than CK levels (in 1 to 6 hours), thus have a low negative predictive value and may not be used as a ruling out test. Secondly, myoglobinuria is not always visible, or may be resolved early; it takes a urine myoglobin level of 100mg/dL to cause tea or cola colored urine. Moreover, detecting myoglobinuria is commonly done using urine dipstick tests (ortho-toluidine), which also react with the globin fragment of hemoglobin, thus a nonspecific test (e.g. in hematuria due to erythrocytes or their fragments). Rodríguez-Capote et al. performed a systemic review which proved a high sensitivity but poor specificity of myoglobinuria as a rhabdomyolysis marker\textsuperscript{108}. Immunoassay is more sensitive and specific than dipstick, but often not readily available, and it may take days to obtain results. Thus, serum myoglobin and myoglobinuria are not necessarily sensitive or specific parameters, dependant on many factors.

**Imaging**
Rhabdomyolysis is usually diagnosed as a clinical syndrome, with supporting laboratory tests. However, recent reports claim that, in obscure cases, in which diagnosis is not definite, several imaging tests may prove useful. Bone scintigraphy demonstrates Tc99-labeled diphosphonate reacting with released calcium (due to sarcosomal disruption) in muscle tissue\textsuperscript{109}. Magnetic resonance imaging (MRI) may demonstrate an increased signal using T2 weighted images, a decreased signal using T1 weighted images, and a contrast between healthy and damaged muscles using STIR images (which suppresses fat tissue signal). Computerized tomography (CT) images demonstrate diffuse areas of low attenuation in the muscle and muscular swelling due to edema and defined intramuscular hypodense foci suggesting muscle necrosis. Ultra sound (US) may reveal hypoechoic areas attributed to inflammation and fluid infiltration\textsuperscript{110,111}. All techniques could also detect macroscopic findings of the kidney, if affected. None of these techniques is highly specific to rhabdomyolysis, but MRI has proved to be almost 100% sensitive, as other modalities were inferior\textsuperscript{112}. Often rhabdomyolysis is not diffuse, but is isolated to a specific muscle group. In these cases bone scintigraphy or preferably MRI could demonstrate the affected muscles\textsuperscript{113}, and serve as a decision making tool, when fasciotomy is considered\textsuperscript{110,114}, to avoid unnecessary interventions.

**Investigations for underlying cause**
Diagnosing rhabdomyolysis must be followed by a search for the cause. A careful history and physical examination are crucial, but may not always help in concluding definitively the underlining etiology. In such cases there is not a clear protocol for which tests should be attempted. If drugs or toxins are suspected, toxicological screening should be done. If infection is a possibility, appropriate cultures, complete blood count (CBC) and serological studies should be performed. If an endocrine or a metabolic disorder is suspected, blood chemistry and endocrine assay is to be done to confirm this.

Furthermore, in young patients or in recurrent ER, genetic analysis\textsuperscript{115}, muscle biopsy\textsuperscript{102} and the forearm ischemic exercise test\textsuperscript{118} (revealing myopathies and metabolic disorders) may be indicated, since suspicion of genetic disorders should arise. The susceptibility of any individual to malignant hyperthermia can be detected by performing the caffeine halothane contracture test (CHCT), although currently genetic tests may diagnose it without the need for this invasive procedure\textsuperscript{117}. Magnetic resonance imaging (MRI) had also been proved useful in distinguishing the various etiologies of Rhabdomyolysis.

**Other investigations**
ECG monitoring is essential to detect cardiac arrhythmias related to hyperkalemia or hypocalcemia\textsuperscript{118}. Electrolyte abnormalities related to rhabdomyolysis (e.g. hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia) may be detected using a simple blood chemistry test. Metabolic acidosis could be detected using arterial blood gas analysis. Raised levels of muscle enzymes such as lactate dehydrogenase (LDH), aldolase, carbonic anhydrase III and aminotransferases (particularly aspartate aminotransferase – AST with normal levels of alanine aminotransferase - ALT) can indicate the occurrence of rhabdomyolysis. Elevated levels of troponin subtype I are found in 50% of rhabdomyolysis cases, while it is normal in inflammatory and chronic myopathies, in which troponin T subtype and CK levels are elevated\textsuperscript{2}. In rhabdomyolysis associated kidney injury, the elevation in serum creatinine is often more rapid compared to other causes of kidney injury, especially among muscular young people. In concordance, the blood urea nitrogen (BUN) to creatinine ratio is typically low\textsuperscript{4}. Due to all that, CBC, blood chemistry, liver and kidney function tests, prothrombin time (PT), activated partial thromboplastin time (aPTT), may be useful laboratory tests and should be considered.

**Complications**

**Arrhythmias** may occur due to electrolytes abnormalities, chiefly hyperkalemia and hypocalcemia. Since both abnormalities, as well as others described, can present themselves very early in the pathogenesis involving rhabdomyolysis, especially hypocalcemia of the early phase\textsuperscript{2}, monitoring and early intervention are indicated in order to prevent arrhythmias and cardiac arrest.
Volume depletion is caused by third spacing of intravascular fluid - an influx into muscle tissue, caused by cellular electrolyte abnormalities. Alternatively, this could be caused by crush injury, due to external and internal bleedings. This process facilitates the depletion of available ATP, creating a vicious circle, resulting in further damage, hypovolemia and even hypovolemic shock. The hypovolemia in extensive rhabdomyolysis is comparable to that occurring in patients with major vessel bleeding or with extensive burns (>60% of body surface)48.

Compartment syndrome is caused by the same factors as volume depletion, defined as increased intracompartmental pressure, causing oxygen deprivation of the muscle. The syndrome presents with muscle pain (occasionally out of proportion to observed injury), weakness, paraesthesia or hypoesthesia, pallor and tightness of affected muscles. Note that compartment syndrome may present in a milder manner, when concerning a non-acute occurrence, such as chronic exertional compartment syndrome. A compartmental pressure of over 30mmHg (which can be measured using several invasive applications) for more than 8 hours may cause muscular necrosis, or higher pressures for lesser time may cause permanent neuromuscular damage, meaning future dysfunction of the musculoskeletal systems, contractures, posture and gait disturbances119.

Acute kidney injury (AKI) is very common among Rhabdomyolysis patients, although sometimes it presents only several days after the initial impact. About one third to one half of rhabdomyolysis patients will develop acute kidney injury120, as 7-10% of all occurring acute kidney injury are due to rhabdomyolysis4. The mechanisms are diverse and not fully understood. Firstly, myoglobin has a direct nephrotoxic effect due to its activity as peroxidase-like enzyme, causing uncontrolled oxidation of biomolecules, lipid peroxidation and generation of isoprostanones. The nephrotoxic effect, as cellular damage, is caused also by the unbalanced conversion of the ferrous oxide (Fe2+) of the heme group into ferric oxide (Fe3+), generating hydroxyl radicals121. Secondly, renal vasoconstriction is caused by renin-angiotensin, vasopressin and sympathetic innervation, activated due to depletion of intravascular volume. Other inflammatory factors such as endothelin-1, thorboxane A2 and TNF-α, and the depletion of nitric oxide also contribute to renal vasoconstriction. Thirdly, myoglobin interacting with Tamm-Horsfall protein creates casts (more vigorously in an acidic environment), obstructing the tubuli, along with sloughed destroyed cells from tubular necrosis3-6,120. Acidosis is chiefly caused by the depletion of oxygen from involved tissues, resulting in lactic acidosis. However, the kidney injury most probably will advance the situation rapidly48. Another mechanism is unmonitored usage of loop diuretics122. Acidosis may also be caused directly or secondarily by many of the drugs which cause rhabdomyolysis, as mentioned earlier123. Disseminated intravascular coagulation (DIC) may be initiated by released components of necrotic muscle tissue, resulting in diffuse internal hemorrhagic complications39.

Treatment & Management

Although there are no sufficient level I evidence studies, meaning randomized controlled trials, regarding management of rhabdomyolysis patients, there are many series of retrospective clinical studies, case reports and animal models. The milestones of treatment are vigorous fluid resuscitation, elimination of the underlying cause and prevention of complications.

Prehospital care

Due to hypovolemia and the danger of acute kidney injury AKI, aggressive fluid resuscitation is required. Using a large caliber catheter, infusion of 1.5L/hr of normal saline is needed, in purpose to maintain a production of 200 to 300mL of urine per hour. No Lactate or Potassium containing fluids should be used, due to the risk of Rhabdomyolysis related hyperkalemia or lactic acidosis. Early fluid resuscitation, once a single limb is accessed (e.g. before extraction of the patient from a crushed vehicle, rubble etc. in case of crush injury)48, definitely prior to evacuation to a medical center124, or up to 6 hours after admission125 is reported to reduce the incidence of AKI. The longer rehydration is delayed, the more likely is AKI to develop126,127. In massive crush disasters, several series showed better results (meaning decreased risk that renal replacement therapy will be required in the future) when intravenous rehydration was applied prior to complete extraction of injured patient from the scene, using sometimes only one available limb122,124.

Hospital care

While starting or continuing fluid resuscitation, thorough history and physical examination are needed to identify and manage the underlying disease. Vital signs, urine output and serum electrolytes and CK levels should be monitored continuously, using intensive care monitoring if needed. A urinary catheter should be inserted and urine output should be monitored carefully. In patients prone to heart condition due to preexisting disease or elderly patients, haemodynamic monitoring might be necessary to avoid fluid overload. The chief objective of treatment is to achieve vigorous diuresis and to dilute the toxic products, using aggressive IV rehydration. A 1.5L/hr infusion of normal saline is required for initial resuscitation, followed by 300 to 500mL/hr once hemodynamic stability had been achieved. Aggressive rehydration is needed especially when concerning crush injury for hypovolemia management, administrating both normal saline and blood products. The goals set are urine output greater than 200mL/hr and serum CK levels lower than 1000U/L. Note that the CK level desired is not agreed on by all protocols, and that its serum level will rise only 2-4 hours after the primary injury.
Adding mannitol and bicarbonate with saline hydration is advised in order to prevent acute kidney injury, although yet to be supported by randomized controlled trials. Sodium bicarbonate is used for urinary alkalinization, reducing the nephrotoxic effect of myoglobin, cast obstruction, hyperkalemia and lipid peroxidation\textsuperscript{1,124}. Administration is carried out with either one ampoule (44meq) diluted in 1L of half normal saline or 2-3 ampoules (88-132meq) in 1L of 5% dextrose. A rate of 100mL/hr is recommended in order to maintain urine pH>6.5\textsuperscript{122}. During treatment, serum bicarbonate, calcium and potassium levels should be monitored, along with urine pH. If symptomatic hypocalcemia develops, or urine PH resists treatment for more than 6 hours, alkalinization should be discontinued. In case of iatrogenic metabolic acidosis (serum pH>7.45), caused by sodium bicarbonate, Acetazolamide administration might prove useful, as it enhances urine alkalinization\textsuperscript{122}. Mannitol is suggested to increase renal blood flow and glomerular filtration rate, which helps in preventing obstruction of tubuli by myoglobin casts. Another benefit of osmotic diuresis is the drawing of interstitial fluid back to the intravascular compartment, improving hypovolemia, muscle swelling and nerve compression. It also reduces free radicals' level\textsuperscript{4}. Mannitol is to be administered as 20% infusion, giving a loading dose of 0.5g/kg during a 15 minute period, followed by 0.1g/kg/hr infusion rate. Nevertheless, mannitol is to be administered only once intravascular volume had been restored. It should be avoided with patients with oliguria. Urinary and serum pH levels should be monitored, with acetazolamide added if the serum pH is >7.45 or urinary pH remains lower than 6.0\textsuperscript{39}. However, there are no randomized controlled studies that prove the yield of mannitol in this scenario, and some studies have found no benefit\textsuperscript{128}. It should be considered in light of the risk for osmotic nephrosis, due to renal vasoconstriction and tubular toxicity when mannitol serum level exceeds 1000mg/dL\textsuperscript{129}. During treatment, plasma osmolality and osmolar gap (the difference between measured and calculated serum osmolality) should be monitored, with mannitol discontinued if sufficient diuresis is not achieved, or serum osmolar gap exceeds 55mOsm/kg (equals to 1000mg/dL serum level)\textsuperscript{4,129}. The use of loop diuretics (e.g.,furosemide) or recombinant B-natriuretic peptide (Neseritide) in Rhabdomyolysis is controversial, with some researchers recommending their use and others opposing it, because loop diuretics acidify the urine and as there is not sufficient evidence of their yield in reducing mortality, reducing the need for dialysis, reducing the number of dialysis sessions applied and shortening the time of hospitalization\textsuperscript{130}. However, since it acidifies the urine, it might prove useful in cases of iatrogenic metabolic acidosis caused by excessive use of normal saline infusions\textsuperscript{131}. It has been suggested that treatment with corticosteroids might reduce secondary muscle damage due the inflammatory response following initial muscle damage\textsuperscript{132}.

**Treatment of any reversible cause of muscle damage**

The objective is to stop any progressing muscle destruction. Any toxin, infection, trauma or hyperthermia must be diagnosed and treated as early as possible. Drugs and toxins should be eliminated and detoxified (e.g. gastric lavage, antidotes and/or hemodialysis) if possible, and hypoxia must be corrected. Infections should be treated using a broad spectrum antimicrobial regimen until isolated and diagnosed; surgical eradication of infectious foci should be considered (e.g. abscess drainage, soft tissue debridement or removal of infected foreign body). Muscle compartment syndrome is to be treated with fasciotomy. Hyperthermia is treated with external cooling measures and benzodiazepines to control muscular hyperactivity. In malignant hyperthermia, anesthetics should be discontinued, and the patient should be treated with dantrolene sodium; the usual initial dose is 2.5-4.0 mg/kg, followed by a maintenance dose of 1 mg/kg every four hours for up to 48 hours to avoid reoccurrence of the disease\textsuperscript{39}. Electrolyte and metabolic abnormalities that cause rhabdomyolysis (e.g., hypotension, hypernatremia, hyperglycemia, hypocalcemia, and hypophosphatemia) should be corrected as soon as possible.

**Prognosis**

The prognosis of Rhabdomyolysis is heavily dependent upon the underlying etiology, and the associated comorbidities. Despite the lack of any well-organized prospective studies, the available evidence from case reports and small retrospective studies suggests that rhabdomyolysis, when treated early and aggressively, has an excellent prognosis. Moreover, the prognosis for the recovery of full renal function is also excellent.

**References**


Rhabdomyolysis. The role of diagnostic and prognostic factors


