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RHABDOMYOLYSIS: PREVENTION AND TREATMENT

SUMMARY

Rhabdomyolysis (RM) was originally described in patients with crush injury, but non-traumatic causes are also common. A high index of suspicion is necessary to allow prompt recognition and treatment to avoid the development of acute renal failure (ARF) and need for hemodialysis. Classically, RM is treated with fluid administration and diuretics as well as bicarbonate therapy in an attempt to alkalinize the urine. More recently, these adjuncts have come into question and it appears that prompt recognition and appropriate

RECOMMENDATIONS

- **Level 1**
 - **None**
- **Level 2**
 - **Lactated Ringers solution is the fluid of choice when attempting to maintain adequate urinary output (1.0 mL/kg) in patients with rhabdomyolysis (RM).**
- **Level 3**
 - **In patients with RM with low urine output unresponsive to fluid administration alone or a creatinine kinase of 10,000 u/L, alkalinization of the urine and addition of mannitol is warranted.**
 - **In patients with RM, it is important to minimize other potential renal insults (such as nephrotoxic antibiotics, intravenous contrast media, ACE inhibitors, NSAIDS, etc...).**
 - **Serial CK measurements to monitor the resolution of RM are not warranted after the zenith is reached;**

volume replacement is all that is needed to avoid renal deterioration.

INTRODUCTION

RM is the dissolution muscle and release of potentially toxic intracellular components into the systemic circulation (1). RM has the potential to cause myoglobinuric ARF in 10-15% of such patients. Overall, 10-15% of ARF in the United States is from RM.

Creatine phosphate (CP) is found in striated muscle and is a reservoir of high-energy phosphate bonds. Creatine phosphokinase (CPK) catalyzes the regeneration of adenosine triphosphate (ATP) from the combination of CP with adenosine diphosphate (ADP). In RM, muscle cells die and release the CPK enzyme into the bloodstream.

Myoglobin (MG) is an oxygen binding protein that composes 1-3% of the dry weight of skeletal muscle. It has a high affinity for oxygen accepting oxygen molecules from hemoglobin in the bloodstream. With

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

muscle damage, free MG in the blood leads to myoglobinemia. Normally, low levels are well tolerated and are cleared by the reticuloendothelial system. At high levels, however, binding and normal clearing mechanisms become saturated, eventually leading to myoglobinuria and the potential for renal injury and ARF. Myoglobinuria is the presence of MG in the urine. The urine is found to be “positive” for blood despite the absence of erythrocytes on microscopic examination. MG contains iron, the toxic effects of which are described below. MG also has the potential to release vasoactive agents such as platelet activating factor and endothelins which may lead to renal arteriolar vasoconstriction, thus worsening renal function. MG appears first in the plasma, but is rapidly cleared within 24 hours. CPK appears a few hours later than MG, reaches its peak value within the first 24 hours, and remains at such levels for several days. CPK is considered to be a more useful marker for the diagnosis and assessment of the severity of muscular injury due to its delayed clearance from the plasma.

A prerequisite for the development of this disease process is muscle injury, the causes of which are numerous and outlined below. While low levels of ischemia (< 1.5 hours) are typically well tolerated, as the ischemic time lengthens irreversible muscle damage occurs allowing the release of toxic metabolic byproducts. Reperfusion after a period of ischemia contributes to localized tissue edema mediated by leukocytes, leukotrienes and inflammatory mediators. Cell membranes are damaged, cellular contents leak, and intracellular ATP, the main fuel for cellular membrane pumps, is depleted worsening cellular homeostasis. Another problem is the development of intracellular hypercalcemia leading to the activation of intracellular autolytic enzymes that damage cell membranes leading to the cells vulnerability to oxygen free radicals with reperfusion.

There are various causes of RM: vascular interruption, ischemia-reperfusion, crush injury, improper patient positioning, alcohol ingestion, seizures, extreme exercise, electrical injury, infection, hyperthermia, and steroids and neuromuscular blockade (especially in combination). With heightened suspicion for this disorder, non-traumatic causes are being seen with increasing frequency.

A special group that has recently been seen to be at risk is bariatric surgery patients. RM is increasingly being seen in clinical practice as the popularity of bariatric surgery is gaining momentum. Several longitudinal studies have found rates of RM after bariatric surgery ranging from 7-77%. A rare syndrome leading to RM specifically related to these patients is known as gluteal compartment syndrome.

PHYSIOLOGICAL BASIS OF TREATMENT MODALITIES

The most important component with regard to the treatment of patients with RM is the ability to recognize the disease process in a timely fashion to prevent the consequences of myoglobinuria. Worsening renal function as evidenced by increasing blood urea nitrogen (BUN) and creatinine, oliguria, classic “tea colored urine”, and an elevated serum CPK level all but make the diagnosis. Other findings include hypocalcemia, hyperkalemia and the potential for cardiac toxicity, hyperuricemia, hyperphosphatemia, lactic acidosis, and disseminated intravascular coagulation (DIC) from thromboplastin release.

The cornerstone of treatment is aggressive volume resuscitation and expansion of the extracellular fluid compartment. Other modalities described include the use of bicarbonate in an attempt to alkalinize the urine, mannitol, and iron chelators (deferoxamine). Prompt and aggressive restoration of volume is essential and critical to prevent progression to ARF and the need for renal replacement therapy and its inherent cost, morbidity, and mortality. Volume depletion, hypotension and shock combined with afferent arteriolar vasoconstriction due to circulating catecholamines, vasopressin and thromboxane leads to decreased GFR and deficient oxygen delivery to the renal parenchyma. Volume administration can combat some of these disturbances and also dilutes the MG load and reduces cast formation.

High concentrations of MG in the renal tubules cause precipitation with secretory proteins from the tubule cells (Tamm-Horsfell protein) leading to the formation of tubular casts and resultant tubular obstruction to urinary flow. Acidic urine favors this process hence the *theoretic* benefit of bicarbonate use. These patients are typically already acidotic and have acidic urine. Bicarbonate use increases MG solubility, induces a solute diuresis and can potentially reduce the amount of trapped MG. Complications of overzealous

bicarbonate administration, however, include hyperosmolar states, “overshoot alkalosis” and hypernatremia. The use of Diamox has been used for the development of iatrogenic alkalosis.

MG itself has a direct toxic effect as well. MG contains iron, and this moiety is released when metabolized in the tubule cell. Normally, the iron molecule is metabolized to its storage form (ferritin). With an overwhelming load of MG delivered to the kidney, however, this conversion capacity is overwhelmed leading to increased levels of free iron. Iron subsequently becomes an electron donor leading to the formation of free radicals.

Mannitol has several potentially beneficial qualities. It is an osmotic diuretic with a rapid onset of action. In contrast to loop diuretics which inhibit the Na-K⁺/H⁺ ATPase in the distal tubule cell leading to aciduria, mannitol does not acidify the urine. It is a volume expander, reduces blood viscosity, and acts as a renal vasodilator increasing renal blood flow and leading to increased GFR. Perhaps more importantly, it has been found to be an oxygen free radical scavenger. Free radicals are molecules with an uneven number of electrons and in excess can lead to damage of critical cellular ultrastructural elements, lipid membranes, hyaluronic acid and even DNA. Free radicals lead to lipid peroxidation resulting in increased permeability, cellular edema, calcium influx, cell lysis and release of MG, further perpetuating the clinical syndrome of RM.

Another key element in the treatment and prevention of renal failure that deserves mention is the avoidance of other iatrogenic renal insults such as the use of nephrotoxic antibiotics, IV contrast medium, ACE inhibitors, NSAIDs and so forth.

LITERATURE REVIEW

Ron et al. in 1984 published a review of seven patients treated for crush injuries suffered after the collapse of a building (2). All patients had *clinical* evidence of myoglobinuria. CPK levels were not drawn. The volume of fluid necessary to maintain a diuresis of 300 mL/hr was 568 mL/hr. Mannitol was used (average dose 160 g/d). The average amount of sodium bicarbonate given over the first five days was 685 mEq. The goal was to maintain a urinary pH of > 6.5. Visible myoglobinuria cleared at an average of 48 hours and at no time did patients have a creatinine of > 1.5 mg/dL or require hemodialysis. The authors readily admitted that it was impossible to “critically assess the relative beneficial roles of the various components of our regimen” for the lack of a control groups with different treatment protocols.

Homsy et al. in 1997 performed a retrospective analysis of patients with RM at risk for ARF (3). They compared groups receiving saline (n=9) vs. saline, bicarbonate and mannitol (SBM) (n= 15). Twenty-four patients were evaluated over a four year period. There were no differences in the amount of saline infused (204 vs. 206 mL/hr) or urinary output (112 vs. 124 mL/hr) over the first 60 hours between the two groups. There were no significant differences with respect to age, urea, creatinine, potassium, or bicarbonate levels. There was no ARF (defined as the need for dialysis) in either group. Initial CPK was higher in the SBM group (3351 vs. 1747 U/L; p<0.05). The saline group was found to have a somewhat delayed CK determination (2.7 vs. 1.7 days), already had a good response to saline infusion and therefore did not receive mannitol and bicarbonate thus forming the control group. The delayed measurement was postulated to be the reason for the lower CPK determination in the saline group. The authors concluded that progression to established renal failure can be totally avoided with prophylactic treatment, and that once appropriate saline expansion is provided, the addition of mannitol and bicarbonate therapy seems to be unnecessary.

Brown et al. retrospectively investigated the value of bicarbonate and mannitol in preventing renal failure, dialysis and mortality after post traumatic RM (4). ARF was defined as a peak creatinine of > 2.0 mg/dL. CPK levels were routinely drawn on all patients. Patients with a CK > 5000 U/L (n=382) had a higher incidence of renal failure (19% vs. 8%; p<0.0001). 154 patients (40%) received bicarbonate and mannitol at the discretion of the attending physician. There was no difference in the development of renal failure (22% vs. 18%), need for dialysis (7% vs. 6%), or mortality (15% vs. 18%) between groups receiving bicarbonate and mannitol versus those that did not. Groups were also similar with respect to age, gender

and ISS. The authors concluded that the standard of adding bicarbonate and mannitol therapy should be reconsidered.

McMahon et al. performed a retrospective cohort study of 2371 patients admitted to two large teaching hospitals with CPK levels in excess of 5000 U/L within three days of admission (5). The derivation cohort consisted of 1397 patients from Massachusetts General Hospital, and the validation cohort comprised 974 patients from Brigham and Women's Hospital. The purpose was to develop a risk prediction score for RM leading to ARF. Independent predictors of the need for either renal replacement therapy or in-hospital mortality (the composite outcome) were age, female sex, cause of rhabdomyolysis, and values of initial creatinine, CPK, phosphate, calcium, and bicarbonate. The composite outcome occurred in 19.0% of patients (8.0% required RRT and 14.1% died during hospitalization). In-hospital mortality was higher in patients with acute kidney injury (22.5% vs 7.1%, $p < .001$) and substantially higher in patients requiring renal replacement therapy (40.0% vs 11.9%, $p < .001$). Admission CPK levels were not found to be predictive of subsequent patient outcome (as has been identified in other studies) (6-9). The composite outcome was increased only with admission CPK levels in excess of 40,000 U/L confirming the insensitivity of such measurements. A score of less than 5 was associated with a risk of the primary outcome of 2.3%, while a score of more than 10 was associated with a risk of 61.2%. The risk score is thus particularly useful in identifying patients at low-risk of either acute kidney injury or in-hospital mortality. It is not as useful in predicting patients at high-risk however. An online calculator for measuring risk is available [here](#).

In a study by Cho et al., lactated ringer's (LR) solution was compared to normal saline (NS) in the resuscitation of patients with doxylamine intoxication and rhabdomyolysis (10). In a cohort of 97 doxylamine intoxicated patients, 28 (31%) were found to have developed rhabdomyolysis, and were randomized to receive either NS or LR as a primary means of aggressive hydration. Mean CK levels of the NS group and the LR group were 3282 IU/L and 4497 IU/L respectively. After 12 hours of aggressive hydration (400 mL/hour), the amount of sodium bicarbonate administration and the frequency administration of diuretics was significantly higher in the NS group. There were no differences in the time taken for creatine kinase normalization and nobody required renal replacement therapy in either group.

Chakravarty et al. performed a review of eleven case reports, two case series, six prospective and three retrospective comparative studies (11). Overall 145 patients with RM were reported following bariatric surgery. In the comparative studies, 87 RM patients were compared with 325 non-RM patients. The RM patients were more likely to be male, had a greater mean body mass index (BMI) (52 vs. 48 kg/m², $p < 0.01$) and underwent a longer operation (255 vs. 207 min, $p < 0.01$) compared to non-RM patients.

Pereira et al. wrote a systematic comparison of a case of gluteal compartment syndrome after bariatric surgery with 3 previous publications for a total of 9 patients (12). Findings included gluteal pain, pale tight swollen buttock, paresthesias and buttock skin breakdown. Five patients developed ARF, three of which resulted in mortality. Risk factors were found to be super-obesity (BMI > 55), operative time > 4 hours, and male gender. The authors concluded that in these high risk patients, routine postoperative CPK and neuromuscular exams may help to identify early signs of gluteal compartment syndrome and RM.

Neilsen et al. studied a decade of patients with rhabdomyolysis, specifically looking at patients with CPK's greater than 10,000 u/l. Such patients were started on a rhabdomyolysis protocol including intravenous mannitol every 8 hours and sodium bicarbonate administration in addition to usual maintenance fluids with Lactated Ringer's solution. They noted a stark improvement in renal injury and failure compared with patients who were not initiated into their protocol (26% vs. 70%) (14)

TREATMENT PRINCIPLES / ALKALINIZATION OF THE URINE

- 1) In patients with significant rhabdomyolysis (CPK \geq 5,000 IU/L) AND acute renal failure (Cr \geq 2.0 mg/dL), maintain a urinary output of at least 100 mL/hour. Invasive hemodynamic monitoring may be necessary to ensure adequate volume resuscitation. If such a diuresis is not possible with saline alone, add sodium bicarbonate and mannitol as outlined below until a steady trend towards normalization of CPK is established or until the CPK level is below 5000 IU/L or urinary output averages > 100 mL/hour for 12 consecutive hours. In addition to the patient's maintenance IVF (Lactated Ringer's solution), add:
 - a. In patients with a serum sodium \leq 147 meq/L:

- ½ NS with 100 mEq NaHCO₃ / L @ 125 cc / hour
 - b. In patients with a serum sodium > 147 meq/L:
 - D5W with 100 mEq NaHCO₃ / L @ 125 cc / hour
- 2) Administer Mannitol, 12.5 g IV q 6 hours.
 - 3) In patients receiving bicarbonate, check a daily ABG.
 - a. For a pH of ≤ 7.15 or a serum bicarbonate of ≤ 15 mg/dL bolus with 100 mEq NaHCO₃ and recheck ABG in 3 hours and repeat until the pH is > 7.15 AND the serum bicarbonate is > 15.
 - b. Discontinue bicarbonate infusion if pH ≥ 7.50.

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