

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

RHABDOMYOLYSIS : PREVENTION AND TREATMENT IN CRITICALLY ILL PATIENTS

SUMMARY

With an increasing knowledge and understanding of the disease, rhabdomyolysis (RM) is being seen with increasing frequency. A disease originally described in patients with crush injury, more and more non-traumatic causes are being elucidated. A high index of suspicion is necessary to allow prompt recognition and treatment to avoid the most dreaded consequence: the development of acute renal failure (ARF) and the need for dialysis. Classically, the process was treated with fluid administration and various diuretics as well as bicarbonate therapy in an attempt to alkalinize the urine. Most recently, these adjuncts have come into question, and it appears that prompt recognition and aggressive volume replacement is sufficient to avoid renal deterioration.

RECOMMENDATIONS

- **Level 1**
 - **None**
- **Level 2**
 - **None**
- **Level 3**
 - **In patients with RM and good urinary response to fluid administration, alkalinization of the urine with sodium bicarbonate and diuresis with mannitol is unnecessary.**
 - **Unless there is a danger of hyperkalemic arrhythmia, calcium infusion is not indicated.**
 - **In patients with RM, it is important to minimize other potential renal insults (nephrotoxic antibiotics, intravenous contrast medium, angiotensin converting enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), etc...).**

INTRODUCTION

RM has been described as the “dissolution of sarcolemma of muscle and the release of potentially toxic intracellular components into the systemic circulation and the attendant consequences.”¹ RM has the potential to cause myoglobinuric ARF. The incidence of ARF in RM is between 10 and 30%, and 10-15% of ARF in the United States is from RM.

Elevation of CPK is seen in this disorder and its level has been seen to correlate with the development of ARF.² Creatine phosphate (CP) is found in striated muscle and is a reservoir of high energy phosphate bonds. CPK catalyzes the regeneration of ATP from the combination of CP with ADP. In RM muscle cells die and release this enzyme into the bloodstream.

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.

Myoglobin (MG) is an oxygen binding protein that comprises 1-3% of the dry weight of skeletal muscle. It has a high affinity for oxygen and accepts oxygen molecules from hemoglobin in the bloodstream. With muscle damage, free MG in the blood leads to myoglobinemia. Normally, low levels are well-tolerated and are cleared by the reticuloendothelial system, but at high levels, binding and normal clearing mechanisms are 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 dipstick "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 that may lead to renal arteriolar vasoconstriction thus worsening renal function.

A prerequisite for the development of this disease process is muscle injury, the causes of which are numerous and outlined below. Low levels of ischemia (< 1.5 hours) are typically well tolerated, however 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 cell's vulnerability to oxygen free radicals with reperfusion.

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

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 evident by increasing 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 sodium 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 acute renal failure 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 glomerular filtration rate (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 tubular 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 sodium 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 are possible with overzealous bicarbonate administration, however, and 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,

however with an overwhelming load of MG delivered to the kidney such 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 an 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 7 patients treated for crush injuries suffered after the collapse of a building.³ All patients had *clinical* evidence of myoglobinuria. CPK levels were not drawn. The volume of fluid necessary to maintain a diuresis of 300cc/hr was 568cc/hr. Mannitol was used (average 160 gm/day). The average amount of sodium bicarbonate given over the first 5 days was 685 mEq. The goal was to maintain a urinary pH of > 6.5. Visible myoglobinuria cleared on an average of 48 hours and at no time did patients have a creatinine of > 1.5 mg/dL and no patient required 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.⁴ They compared groups receiving saline (S) (N: 9) vs. saline, bicarbonate and mannitol (SBM) (N: 15). 24 patients were evaluated over a 4 year period. There were no differences in the amount of saline infused (204 vs. 206 cc/hr) or the urinary output (112 vs. 124 cc/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 in either group defined as the need for dialysis. Initial CPK was higher in the SBM group however (3351 vs. 1747; p<0.05). The S 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 S 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 association of mannitol and bicarbonate seems to be unnecessary.

Brown et al. in 2004 presented retrospective data at the ACS COT meeting which was recently published.⁵ The purpose was to investigate the value of bicarbonate and mannitol in preventing renal failure, dialysis and mortality after post traumatic RM. ARF was defined as a peak creatinine of > 2.0 mg/dL. At their institution CPK levels are 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 (40%) received bicarbonate (B) and mannitol (M) at the discretion of the attending physician. There was NO DIFFERENCE in renal failure (22% vs. 18%), dialysis need (7% vs. 6%), or mortality (15% vs. 18%) between groups receiving B and M and those 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.

Meijer et al in 2003 published data regarding the prognostic usefulness of a serum CPK determination.² It was a retrospective review of 30 patients with a CPK > 10,000 U/L over a 5 year period. The purpose

was to identify the laboratory and clinical parameters that would predict the onset of ARF in patients with severe acute RM. ARF was defined as the need for renal replacement therapy. In this group renal failure was seen in 17 (65%) of patients. Admission and peak CPK levels correlated with ARF: admission CK (IU/L) 47194 vs. 17531 (p=0.0153); peak CK (IU/L) 55366 vs. 28643 (p=0.0272). CK values declined faster in patients without renal failure. The authors concluded that CK levels may be useful as a prognostic tool.

Knottenbelt in 1994 published a retrospective review of 200 patients that sustained beating and found the following to correlate with the development of ARF: late presentation, high CPK levels (13,603 in the oliguric ARF group vs. 2194 in the non-ARF group), initial low hemoglobin, heavy pigmenturia and severe acidosis.⁶

REFERENCES

1. Visweswaran P, Guntupalli J. Rhabdomyolysis. *Critical Care Clinics* 1999; 15:415-428.
2. Meijer AR, Fikkers BG, Keijzer MH, van Engelen BGM, Drenth JPH. Serum creatine kinase as predictor of clinical course in rhabdomyolysis: A 5-year intensive care survey. *Intensive Care Med* 2003; 29:1121-1125.
3. Ron D, Taitelman U, Michaelson M, Bar-Joseph G, Bursxtein S, et al. Prevention of acute renal failure in traumatic rhabdomyolysis. *Arch Intern Med* 1984; 144:277-280.
4. Homsí E, Barreiro M, Orlando JMC, Higa EM. Prophylaxis of acute renal failure in patients with rhabdomyolysis. *Renal Failure* 1997; 19:283-288.
5. Brown C, Rhee P, Chan L, Evans K, Demetriades D, Velmahos G. Preventing renal failure in patients with rhabdomyolysis: Do bicarbonate and mannitol make a difference? *J Trauma* 2004; 56:1191-1196.
6. Knottenbelt JD. Traumatic rhabdomyolysis from severe beating - experience of volume diuresis in 200 patients. *J Trauma* 1994; 37:214-219.