Rhabdomyolysis – Go big or go home

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Abstract

Objective: To evaluate the occurrence of renal injury in hospitalized patients with the diagnosis of rhabdomyolysis among a series of patients presenting to an urban emergency department.

Methods: A retrospective chart review between January 2006 and February 2017 was conducted on patients aged 21–65 years old that were admitted with a diagnosis of Rhabdomyolysis. We included patients with an initial serum creatinine (Cr) level < 1.3 mg/dL and an initial serum creatine phosphokinase (CPK) level > 1000 U/L. We excluded patients with preexisting renal disease, hypertension, diabetes, patients currently on medications in the statin class, patients with muscular dystrophy and neuromuscular disorders.

Results: One hundred and fifteen patients (100 men, 15 women) were enrolled, with a mean age of 36 years old. The mean CPK at presentation was 18,965 U/L and the highest CPK was 168,300 U/L. The mean Cr upon presentation was 0.95 mg/dL. The average length of stay of our patients was 4.6 days. The longest length of stay was 30 days and the shortest was 1 day. Seven patients had hospital stays longer than 10 days. None of the patients had prolonged admissions due to rhabdomyolysis alone. The patient admitted for 30 days had a protracted admission due to liver failure and sepsis thought to be unrelated to Rhabdomyolysis. No patients that fit our inclusion criteria developed renal insufficiency (Cr > 1.3 mg/dL) or failure regardless of their CPK upon presentation, peak CPK or therapies received during their hospitalization.

Conclusion: Patients in our data set that presented to the Emergency Department with a CPK of >1000 U/L and a Cr of <1.3 mg/dL that were hospitalized with a diagnosis of rhabdomyolysis are not at risk for developing renal insufficiency or failure if treated promptly with fluid rehydration, regardless of their initial CPK values.

1. Introduction

The term rhabdomyolysis comes from the Greek words rhabdo, meaning “rod or spindle like”, myo meaning “muscle”, and lysis “dissolution or destruction”. Rhabdomyolysis is the breakdown of skeletal muscle with the release of its cellular contents into the systemic circulation. The etiologies of skeletal muscle insult leading to rhabdomyolysis are varied and often multifactorial. Causes may include direct muscle injury from crush syndrome, pressure necrosis, electric shock, freezing or burns, excessive exercise, ischemic necrosis from vascular occlusion or external compression, metabolic disorders, sepsis, inflammatory myopathies, hereditary disorders, medications, drugs of abuse, alcohol and various other toxins. Regardless of the etiology, the common pathway in rhabdomyolysis is an increase in intracellular calcium leading to the lysis of skeletal muscle cells and the release of intracellular contents [1-3].

A consequence of release of intracellular muscle contents is the potential development of renal injury or renal failure. Historically, crush injuries resulting in renal injury have been reported as early as 1941 when Bywaters and Beall observed this condition after the bombings of the Battle of Britain [4]. At that time the mechanism underlying renal injury was not elucidated. The current medical literature suggests that there are 3 pathogenic mechanisms involved in rhabdomyolysis-induced acute renal injury and failure. These include myoglobin cast formation in the distal convoluted tubules, direct cytotoxic action of myoglobin on the epithelial cells of the proximal convoluted tubules, and intrarenal vasoconstriction and ischemia [5].

CPK is an enzyme found in the mitochondria and cytoplasm of various tissues throughout the body including, skeletal and cardiac muscle, and brain tissue. The release of CPK resulting in a level approximately 5 times the upper limits of the reference range, approximately 1000 U/L, is considered confirmatory for the diagnosis of rhabdomyolysis. Typically, CPK levels rise within 12 h of muscle injury, peak in 24–36 h, and decrease at a rate of 30–40% per day, returning to baseline levels 3–5 days after cessation of
the injury. Myoglobin (Mb) is a dark-red, monomeric heme protein, which binds iron and oxygen, and is found in the muscle tissue. Mb is filtered by the glomerulus and is excreted into the urine and unpredictably eliminated by hepatic metabolism. After its release, plasma levels of Mb rapidly fall, typically reaching its peak in 8–12 h, and then returning to normal within 24 h. When visible in the urine, myoglobin invades a red-brown, or tea color, and will typically be detected on urine dipstick as blood with few or no red blood cells seen on microscopy.

The cornerstone of treatment for rhabdomyolysis is thought to be early and vigorous extracelluar volume expansion. It has been suggested that alkalization of the urine with sodium bicarbonate or the administration of mannitol may minimize renal damage due to rhabdomyolysis. The proposed benefit of sodium bicarbonate is based on observational animal data that myoglobin and ferric heme precipitate in acidic urine and may form casts resulting in tubular obstruction. However, this is a practice that has not been shown to definitively aid in the prevention of renal insufficiency or failure and there is data that suggests that volume expansion alone will prevent the progression to renal failure without an added benefit from the addition of sodium bicarbonate or mannitol. Mannitol and the fluid shifts it induces come with added risks including, pulmonary edema, metabolic acidosis, hypertension, and hyperkalemia.

Given the early release of MB and its purported role in the development of renal toxicity, it is the authors’ contention that if a patient present to the Emergency Department with an elevated CPK, and at the time of presentation they do not have evidence of renal injury, that they are not at risk of developing renal injury or failure. To test this hypothesis we identified the occurrence of renal injury in patients admitted with a diagnosis of rhabdomyolysis and noted the treatments that were administered during hospitalization.

2. Methods

We conducted a retrospective chart review of our institutions electronic medical record, MedHost and identified patients hospitalized with a diagnosis of rhabdomyolysis from January 2006 until February 2017. This was a single institution Institutional Board Review approved study conducted at an urban University Medical Center that has an annual Emergency Department census of over 160,000 patients. We included patients aged from 21 to 65 years of age. We excluded patients with preexisting renal disease, hypertension, diabetes, patients currently on medications in the statin class, patients with muscular dystrophy or neuromuscular disorders.

3. Results

We reviewed 1000 patient charts for which one of the admitting diagnoses was rhabdomyolysis. Of those 1000 charts, 115 patient visits fit our inclusion criteria, with a mean age of 36 years old. 100 of the admissions were male patients, and 15 were female patients. The 3 most common causes of rhabdomyolysis in the patient population we studied were substance abuse, strenuous activity, and seizures, with substance abuse being the most common precipitant. The mean CPK upon presentation was 18,965 U/L and the highest CPK value upon presentation was 168,300 U/L. The initial CPK values ranged from 1018 to 168,300 U/L, and the median CPK at presentation was 5508. The mean creatinine upon presentation was 0.95 mg/dL, with a range of 0.46–1.3. The average length of stay of our patients was 4.6 days, with a median of 3 days. The longest length of stay was 10 days. 89 patients had a hospital stay 5 days or shorter. None of the patients had prolonged admissions due to rhabdomyolysis alone. The patient with the longest admission, 30 days, had a protracted admission due to liver failure and sepsis thought to be unrelated to rhabdomyolysis. The patients in our study stayed in the hospital having repeat CPK values checked to ensure they were trending down appropriately. There was no specific trend or percent decrease in CPK value which was used to deem patients safe for discharge. Some patients CPK values were trended all the way down to the normal range, while others had only one repeat CPK level, and if the value had decreased, no additional CPK levels were obtained. This may be due to differences in practice by the various internal medicine and nephrology providers who treated the patients included in our study.

109 of our patients were treated solely with intravenous (IV) fluid hydration, the remaining 6 patients were treated with a combination IV fluids and sodium bicarbonate. Due to a change in electronic medical record, exact IV fluid amounts were only able to be analyzed for 63 of our 115 included patients. Of those 63 patients, a mean of 3.57 days of IV fluid were administered, with a median of 3 days. The mean amount of IV fluid received per day was 2398 mL. None of the patients that met our inclusion criteria developed acute kidney injury defined as a Cr > 1.3 mg/dL regardless of the CPK level on presentation, peak CPK or therapies received during hospitalization.

4. Discussion

In our study we found that patients having a CPK of >1000 U/L and a Cr < 1.3 mg/dL upon presentation to the Emergency Department that were subsequently admitted for rhabdomyolysis did not develop renal insufficiency or failure during their hospitalization. Our study included patients admitted with what was believed to be idiopathic, drug induced and exertional rhabdomyolysis by nature of our exclusion criteria. Although the baseline creatinine of our patients was not known, and accordingly there may be some degree of renal impairment that occurred, it did not rise to the level of a creatinine >1.3 mg/dL which we used as our marker of renal impairment. The highest level of CPK in our data set was on a male patient with a CPK of 168,300 U/L and a creatinine of 1.2 mg/dL upon presentation. Our results were consistent with a previously published study by Sinert et al. of thirty-five patients who were hospitalized for exercise-induced rhabdomyolysis, none of which developed renal impairment or failure. The average CPK in their patient set was 40,471 U/L and the highest was 167,500 U/L. The aforementioned study included only patients with exercise induced rhabdomyolysis whereas we included all patients that fit our inclusion criteria. Another important distinction is the treatments modalities patients received. Whereas the majority of our patients, 109 (94%), were treated with only intravenous crystalloid fluid replacement, all but one of the patients in the Sinert et al. study were treated with Sodium Bicarbonate diuresis, or Mannitol. Nonetheless, no patient in either study developed renal impairment or failure.

In a study evaluating 475 patients admitted with rhabdomyolysis the authors found that acute renal failure developed in 46% of their subjects. Alcohol and illicit drugs use was the most common etiology accounting for 106 of 163 cases of acute renal failure. 10% of their patients had recurrent rhabdomyolysis, which was thought to be from an underlying myopathy or muscle metabolic defect. This study included patients with a discharge code of myoglobinuria, rhabdomyolysis, myopathy, toxic myopathy, malignant hyperthermia, neuroleptic malignant syndrome and polymyositis and a serum CPK of >975 IU/L. Another study found that the factor that appears to be most predictive of the need for hemodialysis in Emergency Department patients with rhabdomyolysis is an
elevated creatinine of >1.7 mg/dL, while hypocalcemia seemed to be predictive of the development of acute renal failure but not the need for hemodialysis [12]. The use of a CPK of >1000 U/L as a diagnostic indicator of Rhabdomyolysis has its limitations. The correlation of an elevated CPK and the severity of associated renal injury have not been established [13]. Therefore the presumption that a CPK > 1000 U/L as an indicator of rhabdomyolysis and the need for admission for treatment thereof may not be necessary. Rather, the incorporation of renal insufficiency, the presence of hypocalcaemia along with an elevated CPK appear to be more indicative of rhabdomyolysis rather than an elevated CPK used solely to establish the diagnosis. It does not appear that an elevated CPK alone predicts the development of renal injury as a complication of rhabdomyolysis.

Although there may be a belief that urinary alkalization should be used in the treatment of rhabdomyolysis, this was based on an animal model, is subject to controversy and has not been validated in human studies. Volume repletion is believed to be cornerstone of therapy for rhabdomyolysis but no study, to our knowledge, has shown a superiority of intravenous fluids to oral hydration. Furthermore, this rests on the assumption that the patient is volume depleted which is not necessarily generalizable to all patients with rhabdomyolysis. Therefore, it is our assumption, that if a patient presents with normal renal function and an elevated CPK > 1000 U/L, and in our study a CPK of up to 168,000 U/L, the patient is unlikely to develop renal failure if treated with rehydration therapy. We further hypothesize that if these patients can tolerate oral rehydration, they may be candidates for outpatient treatment, however, this has yet to be proven, and should be the focus of a further study.

5. Limitations

The authors acknowledge the limitations of this study. Our results are only applicable to similar patients and by nature of exclusion of patient’s aged less than twenty-one or older than sixty-five we cannot extrapolate our results to include those age groups. We did not attempt to collect information regarding volume status, presence of acidosis or calcium levels. We also did not estimate the creatinine clearance or estimate the time of onset of symptoms and the time of presentation to the Emergency Department. Since the significant majority of our patients were males the generalizability of our results are also limited. We also did not attempt to differ from various racial or ethnic groups. The current belief that volume replacement with intravenous hydration is the optimal treatment for rhabdomyolysis precluded a prospective randomized trial and therefore we felt the best way to study this patient population was retrospectively.

6. Conclusion

We believe that this study is the first to be published using an initial CPK and lack of renal impairment as a negative predictor of the development of renal insufficiency during hospitalization. Although there were only 115 patients in our study, we believe our results effectively demonstrated that our hypothesis has scientific bearing. We also believe that based on the results of this study, the need for hospital admission for patients with rhabdomyolysis based on a CPK > 1000 U/L without other factors necessitating admission should be questioned, and further evaluated. Hence our title “Rhabdomyolysis – Go big or go home”.

Meetings

None.

Grant

None.

Conflicts of interest

None.

Author contributions

This study was conceived by John Kashani. Tyler Manis and Blessit George-Varghese collected the data for the study. Tyler Manis managed and analyzed the data. Tyler Manis and John Kashani drafted the manuscript. Tyler Manis takes responsibility for the paper as a whole.

References