The American Journal of Surgery 214 (2017) 201–206

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Peak creatinine kinase level is a key adjunct in the evaluation of critically ill trauma patients

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ARTICLE INFO

Article history:
Received 12 September 2016
Received in revised form
14 November 2016
Accepted 21 November 2016

Keywords:
Creatinine kinase
Acute kidney injury
Rhabdomyolysis
Trauma
Creatinine

ABSTRACT

Background: Elevated creatinine kinase (CK) can indicate rhabdomyolysis, a risk factor for acute kidney injury (AKI). We investigated risk factors and clinical significance of peak CK levels.
Methods: Retrospective analysis, adult trauma patients. Logistic regression was used to identify risk factors for elevated CK and AKI.
Results: 3240 trauma patients were analyzed; median time to peak CK was 17 h and 347 patients had peak CK > 5000. On multivariable analysis, younger males with severe injury were more likely to have peak CK > 5000 and peak CK > 5000 was an independent risk factor for AKI (AOR 3.79).
Although peak CK levels were significantly lower in older patients (1,637U/L vs 2,604U/L), older patients were more likely to develop AKI at lower CK levels.
Conclusions: CK levels commonly peak within 1–2 days after admission. Despite lower peak CK levels, older patients are more likely to develop AKI. These data may support more rigorous CK monitoring and lower intervention threshold in older patients.

1. Introduction

Creatinine kinase (CK), also known as creatinine phosphokinase or phospho-creatinine kinase, is an enzyme that catalyzes the reversible transfer of phosphate from phosphocreatinine to ADP, forming creatinine and ATP. CK is predominately found in skeletal muscle and is naturally higher in subsets of the population including black race, newborns and males, with reference ranges that vary by temperature and assays.[1] Elevated CK causes include hypothyroidism, celiac disease, viral myositis, strenuous exercise, seizures, muscle injury and multiple medications including statins and antiretrovirals.[1] Elevated CK level is a marker for tissue damage or ischemia, and it is often checked as part of trauma protocol post-fracture or vascular injury. The definition of acute kidney injury (AKI) has evolved from RIFLE (risk, injury, failure, loss, end-stage renal disease) to AKI Network to KDIGO (Kidney disease improving global outcomes)[2] depending on creatinine and urine output metrics. Multiple studies have studied AKI in the trauma population.[3–9] There is evidence that elevated CK is associated with AKI in the post-traumatic population with rhabdomyolysis.[10–12] The postulated mechanism is threefold via renal vasoconstriction, intraluminal cast formation and direct heme protein-induced cytotoxicity.[13] In the trauma population, there is evidence to suggest that CK level of 5000 or higher should raise concern for increased risk of AKI.[10,11] Other studies non-specific to the trauma population have identified thresholds from 500 to 75,000 U/L.[14–19] Renal protective interventions such as bicarbonate and mannitol have theoretic benefit as well as promise in animal studies.[20] So far these are unconfirmed in human studies, potentially related to lack of randomized prospective data resulting in selection bias via sicker patients receiving interventions.[11] Our study aims to evaluate epidemiology of CK levels specifically in the trauma population and identify subgroups particularly at risk for adverse outcomes. We hypothesized that gender could affect the levels of CK levels and that older patients were at higher risk for AKI at lower CK levels.

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http://dx.doi.org/10.1016/j.amjsurg.2016.11.034
0002-9610/

2. Material and methods

After IRB approval, all trauma patients, 17 years and older, admitted to the Los Angeles County + University of Southern California Medical Center (LAC + USC Medical Center) between January 2012 through May 2015 with CK level drawn were evaluated. By protocol all trauma patients admitted to the Surgical Intensive Care Unit have CK levels determined and monitored serially, if elevated. Demographic, physiologic and laboratory data were collected. Patient variables included age, gender, race, associated injuries, vital signs in the field and on admission, mechanism of injury, Glasgow Coma Scale (GCS) in the field and on admission, Injury Severity Score (ISS), history of hemodialysis or chronic kidney disease (CKD), CK and creatinine (Cr) values during hospitalization. Outcomes included mortality, hospital length of stay, Intensive Care Unit (ICU) length of stay and total ventilation days. AKI was defined as peak Cr $\geq$ KDIGO Stage 2 or 3,[21] using baseline creatinine level 2.0 times baseline (upper limit of normal of our lab is 1.0 mg/dL). Urine output data was not available and we elected to not use the Modification of Diet in Renal Disease estimation of glomerular filtration rate assuming 75 ml/min per 1.73 m2 given its limitations in calculating baseline creatinine.[22] Determining a reliable baseline creatinine function in the civilian trauma population will remain difficult given the lack of outpatient prehospital creatinine data[21,23] as well as inability to assume a general level of health without significant comorbidities that may be possible in the military experience. Siew et al. recommend more specific definitions of AKI (KDIGO 2 or 3) to help avoid misclassification when using surrogates for reference serum creatinine.[21] We excluded patients with chronic kidney disease or prior history of hemodialysis.

Use of renal protective maneuvers including sodium bicarbonate or mannitol for rhabdomyolysis is initiated at CK > 5000 by protocol and below that at the treating physician's discretion. Primary endpoint was AKI. Statistical analysis was performed using SPSS for Mac and Windows, version 23.0 (SPSS Inc, Chicago, IL, USA) and R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were compared using two-tailed *t*-test and dichotomous variables were compared using Fisher's exact or Pearson's X^2. Ordinal variables were compared using Mann-Whitney U. Risk factors identified on univariate analysis with statistical significance of $\leq$0.2 were entered into logistical regression analysis and independent predictors were determined. CK Cutoff points were determined using receiver operating characteristic (ROC) curve analysis. Least squared means were calculated by creating a generalized linear regression model adjusting for covariates in R.

3. Results

The study included, 3240 blunt (78%) and penetrating (22%) trauma patients. The median age was 40 years with 1163 patients (36%) greater than or equal to the age of 50 years. The majority (79%) were male with average weight of 80 kg. Most patients, 82.4%, had at least one IV contrast study during their initial trauma workup. Extremity compartment syndrome developed in 0.6% patients and 2.5% underwent prophylactic or therapeutic fasciotomy. Six patients arrived with initial CK > 45,000, (range: 45,037–263,760) and were excluded as outliers from this study. Peak CK was greater than 5000 U/L in 11% of patients (7.9% of penetrating and 11.5% of blunt mechanism). The median time to peak CK level was 17 h overall and 27 h in patients that ultimately peaked over 5000. Patients with peak CK > 5000 were younger, had higher ISS score and higher incidence of fractures when compared to the patients with lower peaks. They were also more likely to undergo fasciotomy and suffer acute kidney injury (Table 1).

On multivariable analysis, independent risk factors for increased CK include younger age (AOR 1.288 per 10 year decrease), male gender (AOR 1.702), black race (AOR 1.951), and higher degree of injury (AOR 1.217 per 5 ISS point increase). Older patients are less likely to reach peak CK > 5000. As age increases, the risk of peak CK > 5000 decreases, for example, for every 10 year increase in age, the risk of elevated CK decreases by 28.8%. Using the young cohort, 17 $\leq$ Age<25 as our reference, we see that patients 50 $\leq$ Age < 75 were significantly less likely to have elevated peak CK (AOR 0.440, $p < 0.0001$), as were patients 75 years and older (AOR 0.071, $p < 0.0001$). Furthermore, increasing injury severity is associated with increased peak CK. For ISS increase of 5 points, the risk of elevated peak CK increases 21.7%. Compared to a reference group of ISS <16, an ISS of at least 16 to 25 had increased odds of elevated peak CK (AOR 1.78, $p < 0.001$) as did ISS >25 (AOR 2.733, $p < 0.001$). With increasing ISS, the risk of elevated CK > 5000 increased significantly (Table 2).

One hundred sixty four patients (5.1%) developed AKI. Patients that developed AKI were older (50 years vs 39 years, $p < 0.001$), had higher ISS (21 vs 14, $p < 0.001$), and higher peak CK levels (1695 U/L vs 897 U/L, $p < 0.001$). On multivariable analysis, correcting for significant variables, age was a significant predictor of AKI (AOR 1.397 per 10 year increase, $p < 0.001$). Patients age 50 and older were more than two times more likely to develop AKI than their younger counterparts (AOR 2.59). In addition, increasing peak CK level was associated with increased risk of AKI (Table 3). With increasing age, patients are more likely to develop AKI.

Despite lower peak CK levels, patients $\geq$ 50 years were more likely to develop AKI at lower CK levels. After adjusting for gender, age, weight and ISS using a generalized linear regression model, adjusted mean peak CK was lower in older (age $\geq$ 50) compared to younger patients (1637 vs 2,604, $p < 0.0001$) (Fig. 1). Additionally, in the subgroup of patients with AKI, older patients had a lower peak CK compared to younger patients (5427 U/L vs 7893 U/L, $p < 0.008$) suggesting that older patients may develop AKI at a lower threshold (Fig. 2). There was a significant difference in the predicted probability of developing AKI in the older patient population (Fig. 3). An older patient with CK of 5000 had the same predicted probability of AKI as a younger patient with CK of 25,000 when all other factors were equivalent. The female population also had lower adjusted mean CK peaks compared to males (1,759 vs 2,308, $p < 0.001$).

Overall, median time to peak CK was 16.7 h and 90% of patients reached their peak CK within 53 h of admission. In patients that ultimately had a peak CK > 5,000, the median time to reach a CK greater than 5000 was 13.4 h. Excluding patients who had a surgical intervention within 48 h that may have contributed to an acute CK elevation, 90% of patients reached the CK > 5000 threshold by 37 h after admission.

4. Discussion

The present study, to our knowledge, is the largest cohort to date, evaluating post-traumatic CK levels and the factors determining the peak levels. Although AKI in this population is multifactorial, CK > 5000 was identified as an independent predictor of injury. Rhabdomyolysis results from muscle injury from post-traumatic causes including crush injury, electrical injury, compartment syndrome, pressure-necrosis secondary to immobilization, ischemia-reperfusion injury, seizure/myoclonus, among others. Elevated myoglobin (and CK) are implicated in renal injury through three inter-related mechanisms 1) direct damage via casts, 2) ischemia-reperfusion injury and 3) iron-mediated proximal tubule cytotoxicity leading to acute tubular necrosis.[13] Previous