Myoglobin as a Prognostic Factor in Trauma Patients

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Purpose: To describe the association of serum myoglobin and creatine kinase (CK) with prognosis in trauma patients.

Methods: We evaluated 108 trauma patients older than age 15 years who received treatment in the Department of Trauma Surgery from January 2012 to December 2012. Myoglobin and CK serum levels were measured during the week after injury.

Results: The average age of the 108 patients (80 [74.1%] men and 28 [25.9%] women) was 49.8 years. Sixteen (14.8%) developed complications and eight (50.0%) developed acute kidney injury (AKI). All patients with AKI underwent hemodialysis, and six died. Higher serum levels of myoglobin and CK were associated with AKI. Twelve patients died during the study period, and myoglobin and CK serum levels were higher in non-survivors. Of these two factors, myoglobin serum level was independently predictive of death.

Conclusion: In trauma patients, higher serum levels of myoglobin and CK were found to be associated with AKI and death. Higher serum levels of myoglobin were influential for predicting death. (*J Acute Care Surg* 2014;4:73-78)

Key Words: Wounds and injuries, Myoglobin, Creatine kinase, Acute kidney injury

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Introduction

Myoglobin reversibly combines with oxygen and stores oxygen primarily in muscle tissue [1]. Myoglobin is released into the blood and undergoes metabolic change when muscular tissue is damaged, which affects renal epithelial cells, and causes acute kidney injury (AKI) [2,3]. Creatine kinase (CK) is an enzyme found in cells, and is used to convert adenosine triphosphate into adenosine diphosphate. CK is found particularly in skeletal muscle.

Muscular damage-related factors usually measure higher than normal in trauma patients but this depends on trauma severity. About 3~15% of patients with atraumatic rhabdomyolysis and

30% of patients with traumatic rhabdomyolysis show increased serum levels of myoglobin and CK and develop AKI [3].

Many researchers have conducted studies on prognostic factors of trauma patients, but there are few direct studies about AKI and death in association with serum levels of myoglobin and CK.

Therefore, we investigated the serum levels of myoglobin and CK in trauma patients and their utility as prognostic factors for predicting mortality.

Methods

A total of 108 trauma patients older than 15 years, who

received hospital treatment for trauma at Chonnam National University Hospital from January 2012 to December in 2012, was included. Patients who died in 24 hours were excluded. An emergency exploratory laparotomy, interventional procedures, or conservative treatment were provided according to the patient's vital signs and test results. The serum levels of myoglobin and CK were measured every 24 hour until which were normalized. The normal range of myoglobin and CK was 10.2 to 92.5 ng/ml and 35 to 172 U/L respectively. AKI was diagnosed by the risk, injury, failure, loss, end-stage renal disease criteria and all of patients with AKI received continuous renal replacement therapy [4,5]. All patients were observed for demographic data, transfusion, Injury Severity Score (ISS), complications, and clinical outcomes.

We compared the patients who developed AKI with the other patients. In addition, a comparative analysis of clinical factors was conducted about mortality by dividing the patients into non-survivor and survivor groups. Student's t-test, the Mann-Whitney U-test, Fisher's exact test, receiver operating characteristic (ROC) curves, and a logistic regression were conducted using IBM SPSS Statistics ver. 19.0 (IBM Co., Armonk, NY, USA). Variables with a statistical $p < 0.20$ in a univariate analysis were entered into a multivariate analysis, and $p < 0.05$ were considered significant.

Results

Clinical Characteristics of the Patients

Demographics and clinical characteristics of the patients were outlined in Table 1. The average age of the 108 patients was 49.8 years (80 men [74.1%] and 28 [25.9%] women). The average hospitalization was 16.4 days and the average hospitalization in the intensive care unit (ICU) was 3.7 days. Ninety-seven (89.8%) patients had blunt injuries, and 11 (10.2%) had penetrating injuries. An emergency exploratory laparotomy was conducted in 63 (58.3%) patients and conservative treatment was provided for 45 (41.7%); 12 of the 45 patients (26.7%) received an interventional procedure. A total number of 16 (14.8%) patients developed a complication; eight of them had AKI and eight had a pancreatic pseudocyst,

intraperitoneal infection, or delayed bowel perforation. All eight patients with AKI underwent hemodialysis and six died. A total number of 12 patients died during treatment. Among them, nine patients received an emergency exploratory laparotomy, and three received an interventional procedure.

Comparisons between the Non-AKI Group and AKI Group

We summarized the results about comparisons between the non-AKI group and AKI group in Table 2. Age, red blood cell (RBC) transfusion volume, ICU length of stay in the AKI group were higher than those in the non-AKI group. Especially, for most of seven days after damage, serum levels of myoglobin in the AKI group were significantly higher than those in the non-AKI group. CK concentrations were higher than non-AKI group for all days; however, it was statistically significant on 5th and 7th day after damage.

Table 1. Patient clinical characteristics

Characteristic	Total (n=108)
Gender	
Male	80 (74.1)
Female	28 (25.9)
Age in years	49.8±16.4
Injury mechanism	
Blunt	97 (89.8)
Penetrating	11 (10.2)
Hospital stay in days	16.4±11.5
Intensive care unit stay in days	3.7±8.0
Injury Severity Score	15.5±9.2
Management	
Operation	63 (58.3)
Nonoperative	45 (41.7)
Intervention/conservative	12 (26.7)/33 (73.3)
Complications	16 (14.8)
Acute kidney injury	8 (50.0)
Pancreatic pseudocyst	3 (18.8)
Infection	1 (6.2)
Hepatic aneurysm	1 (6.2)
Small bowel necrosis	1 (6.2)
Perihepatic abscess	2 (12.6)
Mortality	12 (11.1)

Values are presented as number (%) or mean±standard deviation.

Table 2. Comparisons between the non-AKI and AKI groups

	Non-AKI (n=100)	AKI (n=8)	p-value
Age (y)	48.7±16.2	63.3±13.3	0.015
Gender			0.677
Male	73 (73.0)	7 (87.5)	
Female	27 (27.0)	1 (12.5)	
Injury Severity Score	15.0±8.5	22.5±14.1	0.178
Myoglobin (μ g/ml)			
Day 1	620.0±1,326.5	7,136.0±9,941.0	0.106
Day 2	490.0±1,585.9	8,874.0±10,058.0	<0.001
Day 3	468.7±2,446.3	10,088.0±14,788.8	<0.001
Day 5	138.7±288.6	3,251.4±3,108.0	<0.001
Day 7	219.8±703.0	2,111.6±2,780.3	<0.001
Peak	824.5±2,491.7	13,102.6±14,926.5	<0.001
Creatine kinase (U/L)			
Day 1	894.5±1,088.7	2,429.3±3,589.3	0.236
Day 2	1,137.4±1,062.8	4,867.4±8,035.3	0.791
Day 3	1,235.9±2,714.6	5,091.3±5,324.9	0.066
Day 5	1,009.3±3,193.0	2,139.0±2,328.9	0.013
Day 7	1,202.3±4,390.6	1,305.2±945.5	0.023
Peak	1,579.4±2,491.7	5,628.5±7,434.0	0.062
Red blood cell transfusion (U)	3.1±4.7	12.3±17.0	0.031
Intensive care unit stay (d)	2.3±4.5	21.6±10.8	<0.001
Serum lactate (mmol/L)	3.6±3.6	7.6±7.2	0.052

Values are presented as mean±standard deviation or number (%).

AKI: acute kidney injury.

Comparisons between Survivors and Non-survivors

We showed the results about comparisons between survivors and non-survivors in Table 3. Age, ISS, RBC transfusion volume, ICU length of stay, blood lactic acid contents of non-survivors were significantly higher than those of survivors. All Serum levels of myoglobin were significantly higher in non-survivors than those of survivors. CK tended to be higher in non-survivors than those of survivors over one week of treatment. However, they were significant only on 3th, 5th and 7th day after damage.

Independent Predictors for Mortality by a Multivariate Logistic Regression Analysis

We conducted a multivariate logistic analysis using log myoglobin values, as the difference between the maximum and minimum serum myoglobin values was too large, and they were not normally distributed. Regarding other factors, serum myoglobin peak value in non-survivors was influential factor

(p=0.041; odds ratio, 2.6; Table 4).

ROC Curve for Serum Myoglobin, Lactate, CK in Predicting Death

With respect to prediction of the death, ROC statistics revealed the area under the curve of 0.94 for the peak myoglobin levels, 0.74 for the peak CK levels, 0.77 for lactate. A cut off value of serial peak myoglobin was 3,510 ng/ml. Sensitivity was 89% and specificity was 98%, respectively (Fig. 1).

Discussion

Myoglobin, which is a causal factor for AKI, occurs more in muscle and is released into the blood when muscle is damaged [1]. Then, myoglobin undergoes a metabolic change and causes renal damage [6]. CK is an enzyme that occurs in many tissues and cells. An increase of CK in the blood is related to muscle damage such as rhabdomyolysis, acute

Table 3. Comparisons between survivors and non-survivors

	Survivors (n=96)	Non-survivors (n=12)	p-value
Age (y)	47.7±15.7	66.7±11.5	<0.001
Gender			0.504
Male	72 (90.0)	8 (10.0)	
Female	24 (85.7)	4 (14.3)	
Injury Severity Score	14.1±7.4	27.0±13.3	0.001
Myoglobin (μ g/ml)			
Day 1	1,335.1±4,730.2	3,561.0±3,206.4	<0.001
Day 2	1,116.0±4,590.0	5,190.0±4,807.5	<0.001
Day 3	568.2±2,161.7	9,491.8±16,071.4	<0.001
Day 5	269.6±617.7	3,161.7±3,448.7	<0.001
Day 7	180.3±364.8	2,817.0±3,056.0	<0.001
Peak	801.3±3,300.2	11,960.1±12,538.6	<0.001
Creatine kinase (U/L)			
Day 1	1,164.0±1,273.0	1,579.3±2,006.8	0.584
Day 2	1,305.3±1,200.1	2,332.8±3,835.9	0.681
Day 3	1,465.5±3,272.8	3,593.0±4,608.2	0.022
Day 4	1,197.3±3,704.0	2,752.5±2,000.4	0.002
Day 5	1,236.0±4,634.1	1,777.5±1,045.0	0.002
Peak	1,779.3±3,752.9	2,679.4±3,448.2	0.292
Red blood cell transfusion (U)	3.0±3.3	16.4±15.1	<0.001
Intensive care unit stay (d)	3.5±7.1	13.2±17.1	0.002
Lactate (mmol/L)	3.2±2.9	9.2±7.1	0.004

Values are presented as mean±standard deviation or number (%).

Table 4. Independent predictors for death in the multivariate logistic regression analysis

	Odds ratio	95% confidence interval	p-value
LnMG peak	2.600	(1.038 ~ 6.517)	0.041
Acute kidney injury	46.951	(0.445 ~ 4,948.395)	0.105
Age	1.076	(0.973 ~ 1.189)	0.152
Lactate	1.279	(1.076 ~ 1.520)	0.005
Packed red-blood cell trasfusion	1.422	(1.185 ~ 1.707)	<0.001
Injury Severity Score	1.114	(0.938 ~ 1.322)	0.219

LnMG peak: log transformation of peak myoglobin value.

myocardical infarction, and myositis [7]. However, few studies have suggested myoglobin and CK as prognostic factors and researchers have reported somewhat different results. In addition, there are few reports related to trauma patients.

AKI is one of the most severe complications and, in particular, the percentage of cases after trauma varies from 1~31% [8,9]. The causes are an emergent operation, nephrotoxic drugs, low blood pressure, and hypothermia

Fig. 1. Receiver operating characteristic curve for serum myoglobin, lactate, creatine kinase in predicting mortality.

[10,11]. Because of the influence of AKI over clinical course, to predict it is important thing for clinicians. Among many biochemical markers, CK and myoglobin were known to be higher than normal in rhabdomyolysis. In addition, they play important roles for developing renal damage [12]. Some researchers investigated the relation between their concentrations and AKI

in rhabdomyolysis, and showed the various results. Melli et al. [13] showed a positive correlation between peak serum CK and serum creatinine. Kasaoka et al. [14] had failed to show the peak value of CK as a predictor of AKI, but they showed the peak blood levels of myoglobin in the AKI group are higher than the non-AKI group. In addition, they argued that the peak value of myoglobin might predict AKI. Similarly, in our study, myoglobin levels including the peak value were higher in the AKI group rather than the non-AKI group significantly, but CK were not shown that results. However, the results of CK on 5th and 7th day were significant statistically. Considering these results, CK might be influential factor for the prediction of AKI. As referred to earlier, predicting AKI is important. The clinicians will be possible to provide faster renal conservation treatment in the case of high-risk AKI by digitizing it. A study by Shiao et al. [15] reported that if renal replacement therapy was performed faster, prognoses would be better [16,17].

The factors related to the prognosis of trauma patients until now are vital signs during hospitalization, hypothermia, amount of blood loss, increased lactic acid by cyclic degradation and bleeding tendency by coagulopathy [18-20]. Many researchers have conducted studies on prognostic factors of trauma patients, but there are few direct studies about AKI and death in association with serum levels of myoglobin and CK. Myoglobin and CK have been known as useful clinical markers. They are thought to reach the circulation due to disruption of the cellular integrity, and cause systemic reactions depending on the extent and type of damage [12]. Theoretically, that is why we thought to myoglobin and CK as clinical markers making a prognosis.

As a result of comparing the surviving group of trauma patients with the non-surviving group in the present study, in the nonsurviving group, age, ISS, the length of ICU stay, and the serum lactic acid levels were higher. The serum myoglobin levels of all days in the surviving group were higher significantly. However, we failed to show CK differences between the surviving group and the non-surviving group like the former comparison. The results of CK on 3th, 5th and 7th day were only significant statistically. We presumed that

because serum myoglobin peaked earlier than CK, the CK values were not different significantly on 1st and 2nd day. Further studies will be needed.

Additionally, we perform the log-transformation of myoglobin levels because the difference between the maximum and minimum serum myoglobin values was too large and was not normally distributed. Table 4 shows the multiple logistic regression analysis about myoglobin peak levels as independent variables. In this analysis, the peak myoglobin levels were more influential than any other variables as a predictor of survival.

Lactate was known as a useful predictor for trauma mortality [21]. Interestingly, our ROC curves inferred that the value of myoglobin was superior [22] than the other factors for predicting mortality. So, we think that the myoglobin is worth a try for studying as a predictor of mortality. Our study indicates that the peak value of myoglobin can be a good indicator to predict death. Although effective treatment for damaged organs is important in trauma patients, it is very important to grasp the patient's overall status. Occasionally, a patient dies due to AKI or multiple organ dysfunction syndrome even if surgery or other interventions were successful. Survival rate may improve if the doctor realizes patients at high-risk for AKI and provides renal replacement therapy rapidly [13,22,23].

The limitation of this study was the small number of patients, especially, the number of enrolled patients in AKI and the mortality. It could create a selection bias. Additionally, due to the retrospective design, we had some missing data related the value of myoglobin and CK. So, we could not draw definitive conclusions. Although there were some limitations, the value of CK looks like it has relations with AKI, and the value of myoglobin seem to be related to AKI and the mortality.

Therefore, it is necessary to study more patient groups in a larger study and examine the correlation between the serum levels of myoglobin and CK as well as other factors.

Trauma patients had higher levels of serum myoglobin and CK, and it appears that they are related to AKI. Of them, the serum level of myoglobin might be a good marker for predicting AKI and death. The results suggest that the value of increased serum myoglobin and CK in trauma patients might be useful

for predicting the course of patients and planning the relevant treatments.

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