RHABDOMYOLYSIS FOLLOWING CRUSH INJURY IN THE TAIWAN CHI-CHI EARTHQUAKE

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Background: *On September 21, 1999, the Chi-Chi Earthquake, measuring 7.3 on the Richter scale, struck central Taiwan, resulting in 2329 deaths and 8722 casualties. Among the severely injured, rhabdomyolysis was a common occurrence, often resulting in acute renal failure. The purpose of this study was to define the clinical picture of rhabdomyolysis secondary to crush injury in a local area close to the epicenter of a major earthquake.*

Methods: *We retrospectively identified patients with traumatic rhabdomyolysis, defined as a peak level of serum creatine kinase (CK) over 1000 U/L within 2 weeks of the earthquake, diagnosed at the major medical centers in central Taiwan. Patients with elevated serum CK of etiologies other than crush injury were excluded.*

Results: *A total of 95 cases were recruited from six hospitals. There were 60 males and 35 females with a mean age of 37.6 ± 17.3 years. The median time from the earthquake to the time of rescue (T-rescue) was 6.0 h (range: 0.1 to 31 h) and median time to emergency room was 11.0 h (range: 2 to 144 h). The median peak level of serum CK (pCK) was 20000 U/L (range: 1040 to 351540 U/L). Acute renal failure (ARF), defined as a serum creatinine level over 1.3 mg/dl, was found in 52 cases (54.7%). Dialytic therapy was performed in 32 cases (33.7%). Among them, 29 (90.6%) were oliguric with a mean oliguric phase of 11.0 ± 9.5 days (median: 9, range: 1-36 days). Most patients (88 cases, 92.6%) also suffered from at least one of the following associated injuries: fracture (41.5%), neuropathy (29.8%), head injury (10.8%), chest injury (7.5%), abdominal injury (7.4%), and thermal burn (1.1%). Fasciotomy for compartment syndrome was performed in 35 cases (36.8%). Oliguric patients were associated with longer T-rescue (9.85 vs. 5.04 hours, $p < 0.01$), higher pCK (79204 vs. 30495 U/L, $p < 0.01$), higher LDH (4110 vs. 1498 U/L, $p < 0.02$) and lower serum calcium (6.53 vs. 7.46 mg/dl, $p < 0.001$) when compared with nonoliguric patients. The pCK positively correlated with BUN, Cr, AST, LDH, and phosphate (all $P < 0.005$). Besides, the pCK also negatively correlated with serum calcium, blood pH, and urine volume in the first 48 hours (all $p < 0.05$). Although the pCK correlated well with the presence of oliguria and the need for dialysis, there was no correlation between pCK and mortality. Those patients with ARF were associated with a higher mortality (17.3% vs. 0%, $p < 0.02$). Mortality (9 cases, 9.5%) did not correlate well with age, sex, presence of oliguria, need for dialysis, or pCK.*

Conclusion: *The pCK of patients with rhabdomyolysis following crush injury is a reliable prognostic indicator of renal outcome and correlates well with most biochemical parameters. Renal failure was associated with a significantly higher mortality rate. (Acta Nephrologica 2005; 19: 62-67)*

Key words: ***earthquake, rhabdomyolysis, crush injury, acute renal failure, serum creatine kinase***

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INTRODUCTION

Rhabdomyolysis and acute renal failure have been known to follow massive destruction of skeletal muscle cells.[1-3] The precipitation of myoglobin in the renal tubules with secondary obstruction and/or tubular toxicity constitutes the primary cause of acute renal failure (ARF) during myoglobinuria.[4-6] Another important enzyme released into the bloodstream from injured muscle tissue is creatine kinase (CK, creatine phosphokinase). CK is a widespread enzyme that catalyzes the phosphorylation of creatinine into creatinine phosphate. It is predominantly found in the skeletal muscle, cardiac muscle, smooth muscle, and brain, and is classified as three different isoenzymes, CK-MM, CK-MB and CK-BB. The skeletal muscle has a very high CK content, around 98% CK-MM and 2% CK-MB. The peak level of serum CK (pCK) is an excellent marker for the diagnosis of rhabdomyolysis.[5-8] It is present in the serum immediately following muscle injury, peaks at about 12 to 36 hours, and has a half-life of about 48 hours. However, a crush injury does not necessarily result in rhabdomyolysis. Similarly, rhabdomyolysis does not always lead to ARF.[5,6] Dehydration and sepsis are also common causes of acute renal failure following a crush injury or prolonged entrapment after a major earthquake. Moreover, crush injury related to rhabdomyolysis, hyperkalemia, ARF, and hypovolemic shock are the major medical causes of mortality in earthquake injury victims.[3] The link between rhabdomyolysis and mortality is hyperkalemia at the beginning and acute oliguric renal failure and sepsis later.[5-7]

The Chi-Chi Earthquake struck central Taiwan at 1:47AM on September 21, 1999. It registered 7.3 on the Richter scale and resulted in 2329 deaths and 8722 injuries.[9] Most of the injured were crushed or trapped in collapsed buildings. Among those with severe and prolonged limb compression, there were high incidences of rhabdomyolysis, acute renal failure and mortality, despite advanced critical care. The purpose of this study was to define the clinical picture of rhabdomyolysis secondary to crush injury in a local area close to the epicenter of the earthquake. The relationship between the severity of rhabdomyolysis and clinical outcome was also studied.

MATERIALS AND METHODS

Within three months of the Chi-Chi Earthquake, we retrospectively identified all of the patients diagnosed with traumatic rhabdomyolysis (defined by a pCK of more than 1000 U/L within 2 weeks following the earthquake) in most of the nearby reference hospitals (three medical centers and five local hospitals). Patients with elevated serum CK of etiologies other than crush injury were excluded. We analyzed the dimensions of the nephrologic problem, including patients' general demographic data, time to rescue (T-rescue), time to emergency room (T-ER), anatomical injury sites, associated injuries, management and complications during admission, type of surgical interventions, total volume of fluid given in the first hours after admission, first day urine volume after admission, development of oliguria (urine volume < 400 mL/day), need for dialysis, discharge, transfer, mortality, morbidity, and laboratory data. The laboratory data included pCK, creatinine (Cr), blood urea nitrogen (BUN), asparate aminotransferase (AST), lactate dehydrogenase (LDH), potassium (K), phosphate (P), and nadir serum levels of calcium (Ca), bicarbonate, and blood gas pH. ARF was defined as a serum Cr concentration over 1.3 mg/dl in a previously healthy person and/or acute oliguria (urine volume < 400 mL/day).

STATISTICAL ANALYSIS

Statistical analysis was performed using commercially available software for this purpose (SSPS, version 10.0 [SPS Inc, Chicago, IL]). Descriptive statistics for clinical and laboratory data are presented as mean ± standard deviation (SD). Statistical significance was tested using student's t-test, Mann-Whitney *U*-test, chi-square test, one-way ANOVA and linear regression analysis when appropriate. Statistical significance was defined as P value less than 0.05.

RESULTS

Clinical characteristics of patients with rhabdomyolysis following crush injury in the Chi-Chi Earthquake are listed in Table 1. Six hospitals returned completed questionnaires within the first six months of the disaster, and 95 sets of data were collected for analysis. Sixty patients were male and 35 were female. The age ranged from 1 to 75 years, with a mean age of 37.6 years (SD 17.3). The median time from the earthquake to rescue (T-rescue) was 6.0 hours, with a range of 0.1 to 31 hours. The median time to emergency room (T-ER) was 11.0 hours (range: 2 to 144 hours). The median CK level was 20000 mg/dl (range: 1040 to 351540 mg/dl). Fifty-two (54.7%) patients developed acute renal failure, defined as a serum Cr level > 1.3 mg/dl. Thirty-two cases (33.7%) received emergent dialytic therapy, including hemodialysis and/or continuous venovenous hemodiafiltration. Among them, 29 (90.6%) were oliguric (24 hour urine amount < 400 ml). The average duration of oliguric phase in these 29 patients was 11.0 ± 9.5 days (median: 9, range: 1-36 days). None developed chronic renal failure. A total of 88

cases (92.6%) also suffered from at least one of the following associated injuries: fracture (41.5%), motor or sensory neuropathy (29.8%), head injury (10.8%), chest injury (7.5%), abdominal injury (7.4%), and thermal burn (1.1%). Fasciotomy was performed in 35 cases (36.8%) due to compartment syndrome. Eight patients developed superficial infection and another 16 patients suffered deep infection following fasciotomy. Six patients underwent amputation and one patient died of sepsis due to uncontrolled infection of the fasciotomy wound. The laboratory data for patients enrolled in this study are listed in Table 2.

The pCK correlated positively with serum levels of BUN ($r = 0.33$, $p = 0.001$), Cr ($r = 0.34$, $p = 0.001$), AST ($r = 0.47$, $p < 0.0001$), LDH ($r = 0.68$, $p < 0.001$) and P ($r = 0.39$, $p < 0.005$). The pCK correlated negatively with serum calcium ($r = -0.46$, $p < 0.0001$), blood pH ($r = -0.29$, $p < 0.02$), urine volume in the first 48 hours ($r = -0.27$, $p < 0.05$), age ($r = -0.28$, $p < 0.008$), and serum bicarbonate ($r = -0.41$, $p < 0.001$) (Fig. 1). However, the pCK did not correlate with serum potassium level. Moverover, pCK level was well correlated with the presence of oliguria and the requirement of dialysis, but not with mortality, T-rescue, and T-ER (Table 3).

Most patients in our series received vigorous fluid supplement (median: 5240.0 ml, range: 500 to 15381 ml in 48 hours). Various drugs were used in different combinations, including mannitol (18.9%), dopamine (36.8%), sodium bicarbonate (43.2%), and furosemide (55.8%). Sixty-five (68.4%) of the 95 patients were administered more than one drug in addition to hydration therapy. The initial emergency room management included mannitol, dopamine, sodium bicarbonate and furosemide. However, none of the above managements were associated with a shortening of the oliguric phase in oliguric patients. In comparison with nonoliguric patients, oliguric patients showed a longer T-rescue (9.85 vs. 5.04 hours, $p < 0.01$), higher pCK (79204 vs. 30495 U/L, $p < 0.01$), higher LDH (4110 vs. 1498 U/L,

Table 1. Clinical characteristics of patients with rhabdomyolysis following crush injury in the Chi-Chi Earthquake

		Range
Total Number	95	
Male : female	60:35	
Age (years)	37.6 ± 17.3	1-75
Time to rescue (hours)	6.0 (median)	0.1 - 31
Time to emergency room (hours)	11.0 (median)	2-144
Mortality	9 (9.5%)	
Time to mortality (days)	7.0	1-32
Associated injury	88 (92.6%)	
fracture: 39 (41.5%), motor or sensory neuropathy: 28 (29.8%), head injury: 10 (10.8), chest injury: 7 (7.5%), thermal burn: 1 (1.1%)		
Fasciotomy	35 (36.8%)	
Acute renal failure	52 (54.7%)	
Dialytic therapy	32 (33.7%)	
Oliguria	29	
Oliguric phase (days)	11.0 ± 9.5	1-36

Table 2. Biochemical data of patients with rhabdomyolysis following crush injury in the Chi-Chi Earthquake

	N	Median	Range
CK (U/L)	95	20,000	1,040-351,540
Cr (mg/dl)	95	1.62	0.8-12.4
BUN (mg/dl)	95	31.2	8-252
GOT (U/L)	94	344	18-5,300
K (mEq/L)	92	4.8	2.9-8.6
LDH (U/L)	79	921.1	6-23,868
P (mg/dl)	58	4.9	1.2-13.3
Ca (mg/dl)	87	7.1	3.7-9.4
pH	84	7.36	6.93-7.51
Bicarbonate	78	18.9	6.7-26.7

p < 0.02) and lower serum calcium (6.53 vs. 7.46 mg/dl, p < 0.001). Mortality occurred in 9 cases (9.5%) at a median duration of 7.0 days (range: 1 to 32 days). The causes of mortality were sepsis (5 cases), multiple organ injury (3 cases), and head injury (1 case). Mortality did not correlate well with age, sex, presence of oliguria, need for dialysis or pCK level. Those patients with ARF had a higher risk of mortality (17.3% vs. 0%, p <0.02) (Table 4).

DISCUSSION

In a major earthquake, such as the Chi-Chi Earthquake, rhabdomyolysis following crush injury is a major concern. The early detection of life-threatening signs allows for immediate life-saving therapy. Although there are some limitations to this retrospective analysis, its value is that it provides information for improving the prognosis of crush victims in future disasters.

The pCK can reflect the degree of muscle damage following crush injury. In fact, we found that pCK is a good prognostic indicator of renal outcome and correlates well with most of the clinical manifestations and laboratory data (Fig. 1 and Table 3). In accordance with previous findings of Veenstra et al.[6] our study demonstrated that the pCK in most patients with traumatic rhabdomyolysis are only moderately elevated (median pCK = 20000 U/L). Those patients with only mild to moderately elevated pCK had a lower incidence of ARF and severe electrolyte disturbances when compared with patients with highly elevated pCK. We also found that oliguric patients were associated with longer T-rescue, higher pCK, higher LDH and lower serum calcium, when compared with nonoliguric patients. However, mortality was not related to pCK, but was related to the presence of renal failure (Table 3 and Table 4). Many previous reports regarding pCK in patients with traumatic rhabdomyolysis show similar mortality rates.[5,6,10] Indeed, using the same criteria (pCK levels > 1000 U/L) in this present study, Ward et al. reported mortality rates of 42% in their ARF and 8% in their non-renal failure groups.[5]

Another aim of this study was to investigate the relationships between pCK, clinical manifestations and laboratory data. In support of previous reports, the pCK positively correlated with serum levels of BUN, Cr, AST, and serum P. The pCK also negatively correlated with urine volume in the first 24 hours, serum calcium, serum bicarbonate, and blood pH. Again, the pCK did not correlate well with serum potassium level in this study.[6]

Rhabdomyolysis induced renal injury is associated with direct renal tubular toxicity, renal vasoconstriction, and luminal obstruction.[11] This is mainly due to myoglobin related renal injury. Results from in vivo animal studies have shown that the pathogenesis of myoglobin related renal injury is physical blockage of renal tubules induced by the precipitation of hematin.[12] In addition, there is now accumulating evidence that renal injury, caused by lipid peroxidation, is important in the pathogenesis of renal failure.[13-16] The heme cen-

Table 3. Relationship between CK, clinical manifestations

	CK (U/L)				
	≥ 100,000 (n=31)	50,000~99,999 (n=33)	10,000~49,999 (n=16)	<10,000 (n=12)	P value
T-rescue (hrs)	9.2	7.3	6.3	7.1	NS
T-ER (hrs)	18.2	27.8	17.0	20.2	NS
Male (%)	42.9	60.0	70.6	61.8	NS
Mortality (%)	7.1	10.0	9.1	9.1	NS
Oliguria (%)	57.1	60.0	32.3	19.4	0.0265
Dialysis (%)	64.3	70.0	25.7	14.7	0.0003

Table 4. Serum creatinine level predicts mortality

	Serum Cr (mg/dl)		
	> 1.3	< 1.3	P value
Time to rescue (hours)	9.2	4.9	0.006
Time to emergency room (hours)	21.8	17.6	NS
First 48 hours urine volume (ml)	804	2436	0.001
Ratio of male (%)	66.7	57.1	NS
Mortality (%)	17.3	0	0.017

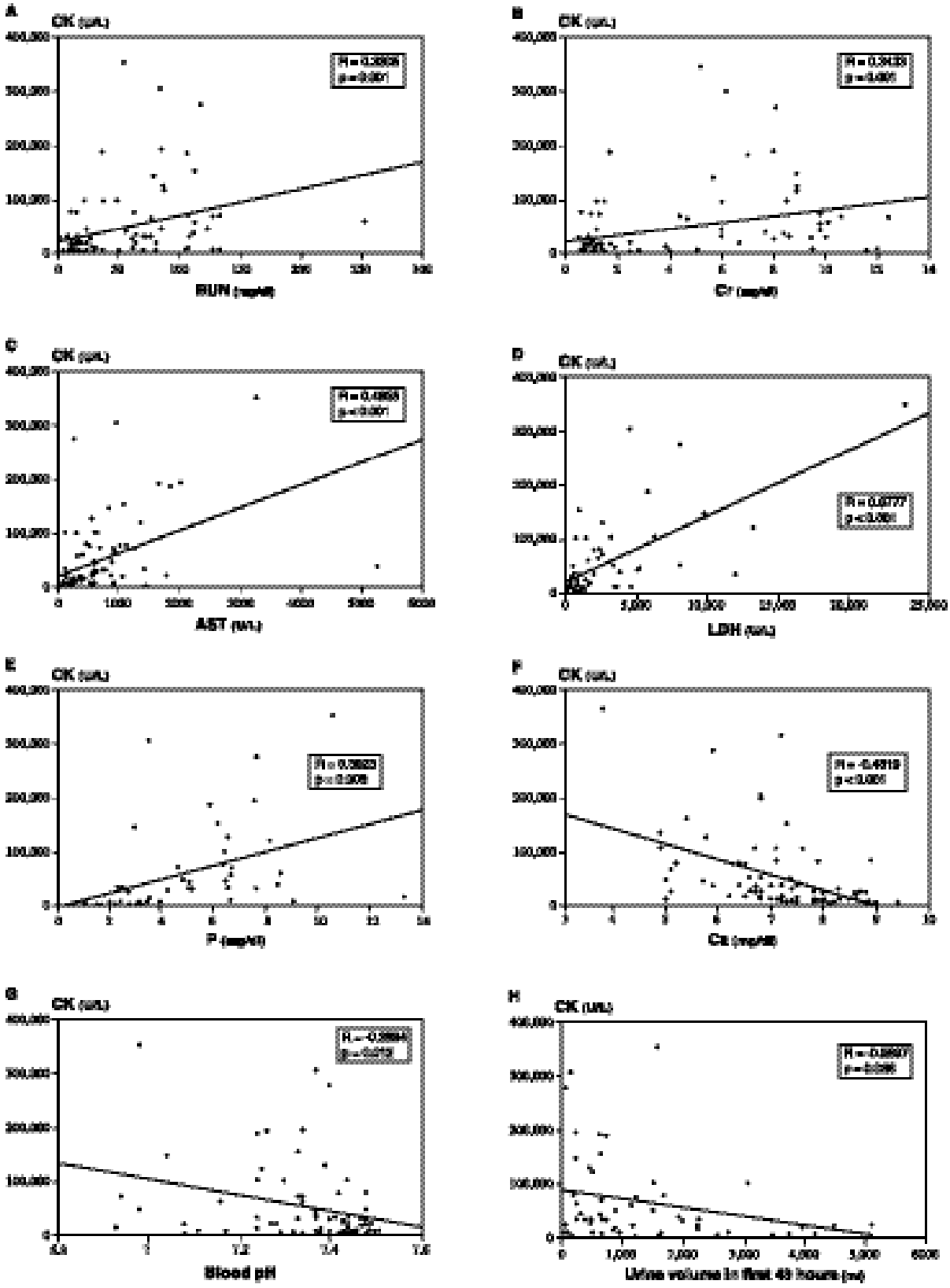

Fig. 1. Correlation of peak level of serum CK and serum levels of BUN, Cr, AST, LDH, P, Ca, blood pH, urine volume in first 48 hours.

ter of myoglobin may initiate lipid peroxidation and renal injury without invoking the release of free iron. This process is due to redox cycling of the heme group from ferrous to ferric and ferryl oxidation states.

Early management of crush victims using vigorous hydration with forced solute alkaline diuresis is very important for reducing the degree of acute renal failure and preventing severe acidosis or hyperkalemia-related mortality. It is clear that vigorous fluid resuscitation can improve renal blood flow and prevent renal failure.[7,8,15,17,18] Moreover, another report demonstrated that alkalinization of urine reduces the injury of myoglobulinuria.[16] Since the alkalinization of urine can stabilize reactive ferryl myoglobin complex by reducing the precipitation of hematin, it may also reduce myoglobin-induced lipid peroxidation.[13] Alkaline solute diuresis can be achieved using sodium bicarbonate and mannitol.[16,19,20] However, bicarbonate may also have potential negative effects. It consists of venous hypercapnia with an increase in mixed venous CO_2, leading to a decline in tissue intracellular pH, a decline in the pH of the cerebrospinal fluid, and finally tissue hypoxia. In this regard, once appropriate saline expansion is provided, the administration of mannitol and bicarbonate seems to be unnecessary.[21] However, this study failed to support the beneficial effect of bicarbonate.

In summary, the serum level of CK is a good prognostic indicator for renal outcome in rhabdomyolysis following a crush injury and correlates well with most biochemical parameters. The development of ARF was associated with a significantly higher mortality rate. The lessons learned from the Chi-Chi Earthquake will help to improve our practical approach in the case of future disasters.

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