EXCELLENT PUBLISHERS

International Journal of Current Research and Academic Review

ISSN: 2347-3215 Volume 3 Number 2 (February-2015) pp. 196-202

www.ijcrar.com

Prevalence of rhabdomyolysis in hospitalized patients in toxicology ward, Sina Hospital, Tabriz, Iran

Ali Ostadi[1], Hamid Noshad[2], Somayeh Jalali[3] and Hosein Eslami[4*]

[1]Department of Forensic Medicine and Toxicology, Department of Internal Medicine, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
[2]Department of Nephrology, Department of Internal Medicine, Sina Hospital, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
[3]General Medicine, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Department of Oral and maxillofacial Medicine, Faculty of Dentistry, Tabriz University of Medical Sciences Tabriz, Iran

Corresponding author

KEYWORDS

Poisoning,
Rhabdomyolysis,
Renal failure

A B S T R A C T

Poisoning is a common cause of hospitalization in young individuals that can lead to rhabdomyolysis. Rhabdomyolysis is a syndrome fallowing rupture of plasma membrane of skeletal muscle cells and release of cellular contents into plasma. The classic triad of rhabdomyolysis includes myalgia, muscle weakness and tea- colored urine secondary to myoglobinuria. Rhabdomyolysis is defined as increase in Creatine phosphokinase(CPK) to five times above the upper limit of normal. According to high prevalence of poisoning in young adults and risk of rhabdomyolysis complications, timely diagnosis and treatment of rhabdomyolysis is necessary to prevent mortality and morbidity. To study the prevalence of rhabdomyolysis in poisoned patients. This study was a descriptive cross-sectional study on 400 patients who were randomly selected among hospitalized patients in toxicology ward of Sina hospital. Required information was derived from the patients' medical records and recorded in designed questionnaires and finally, data were analyzed via SPSS 16. Among 400 patients, 24(6%) had CPK>1000U/L and 3(12.5%) developed renal failure (2.75% of total participants). Prevalence of myoglobinuria was reported 9%, myalgia 2.5%, muscle weakness 4%. Mortality rate in studied patients was 1%. Significant correlation was found between increased CPK with creatinine, liver enzymes, fever and duration of hospitalization but the classic triad of rhobdomyolysis was negative in many patients in this study.

Introduction

Rhabdomyolysis is a syndrome secondary to skeletal muscle cell damage and release of toxic contents of myocytes into the systemic circulation (1). In general, causes of rhabdomyolysis are divided into two groups: hereditory and acquired. Hereditory causes

are generally related to defect in enzymes that are involved in catabolism of macromolecules like carbohydrates and lipids.

Acquired causes are also divided into two categories:

A: Traumatic causes such as crush syndrome, accidents, natural disasters and excessive exercise which leads to direct muscular damage and rupture of sarcolemma.

B: Non-traumatic causes which are more common and include alcohol abuse, seizure, coma, prolonged immobilization, hypothyroidism and drugs like statins, amphetamine, antipsycotics and diuretics. Drugs are the most common non- traumatic causes (2-3).

Rhabdomyolysis may cause due to prolonged immobilization because of decreased level of consciousness, coma, drug poisoning, long-term anesthesia and carbon monoxide (CO) poisoning. Clinical signs of rhabdomyolysis typically include myalgia, muscle weakness and tea- colored urine following myoglobinuria. This triad is only seen in less than 10% of the patients and more than 50% of the patients have no muscular complaint. In severe rhabdomyolysis atypical constitutional symptoms like fatigue, fever, tachycardia, nausea and vomiting may occur (1-5).

Severity of rhabdomyolysis can differ from asymptomatic elevation of CPK to elevated CPK along with acute renal failure, cardiac arrhythmia, compartment syndrome and diffuse intravascular coagulation (DIC).

Acute renal failure and hyperkalemia are the most important complications of rhabdomyolysis which worsen the prognosis and need special attention, although renal failure in many cases, is completely reversible (6). As it was mentioned, several substances including myoglobin, electrolytes, non-protein and protein substances, are released into plasma due to muscle cells necrosis, which detection of these substances in laboratory tests, has a major role in early diagnosis of rhabdomyolysis.

Hemoglobin concentration is 100µg/L in serum and 10µg/L in urine. During rhabdomyolysis, myoglobin releases into plasma from skeletal muscle cells and myoglobinemia occurs.

Low affinity of plasma proteins to myoglobin binding and low molecular weight of myoglobin increases renal filtration of myoglobin. After increasing the myoglobin concentration in plasma, reabsorption capacity of epithelial cells of renal glomerules is increased and myoglobin secretion into urine is decreased to protect kidney from toxic effects of myoglobin. When myoglobin concentration exceeds glomerular reabsorption capacity, excessive amounts of myoglobin appears in urine and myoglobinuria occurs.

In severe cases of rhabdomyolysis, when plasma myoglobin reaches more than 300mg/L, macroscopic myoglobinuria and tea- colored urine appears(7-8).

In rhabdomyolysis, myoglobin level increases within 1-3 hours, reaches peak during 8-12 hours and then within 24 hours after initiation of injury, returns to normal level.

Consequently, hemoglobin detection in plasma or urine is pathognomonic if it is measured at initial phase of rhabdomyolysis syndrome(9).

Elevated CPK is the diagnostic hallmark of rhabdomyolysis. CPK is an enzyme in skeletal muscle cells which acts as an catalyzer in transferring of one phosphate group from creatinine (CP) to adenosine diphosphate (ADP) and production of adenosine triphosphate (ATP) and creatinine(Cr) (10).

Moreover, patients with rhabdomyolysis may be febrile and have leukocytosis, pyuria, hyperkalemia, increased Cr to blood urea nitrogen(BUN) ratio, elevated Serum glutamic oxaloacetic transaminase(SGOT), lactate dehydrogenase(LDH) and succinate dehydrogenase levels in their laboratory tests(9-13).

Diagnosis of rhabdomyolysis is confirmed by elevated serum level of myocyte specific intracellular proteins especially CPK and myoglobin(14-15). There is controversy over the diagnostic level of CPK for rhabdomyolysis and Gabow et al. suggested CPK level more than five times the upper limit of normal (>1000U/L)(9).

Although CPK level can't be used as a prognostic factor of progression towards renal failure, patients with CPK level less than 5000U/L are less likely to progress towards renal failure (16). It has been estimated that 80% of rhabdomylolysis cases in adults, are due to toxic and pharmaceutical factors (17). Welte reviewed many studies and literatures during 45 years and concluded that 62% of causes of rhabdomyolysis, are alcohol and drug overuse (4).

Rhabdomyolysis is a rare syndrome and until now, few studies with large sample sizes have done, therefore it is difficult to accurately determine prognosis and complications of rhabdomyolysis.

Thus, a study on prevalence of rhabdomyolysis in poisoned patients can help to early diagnosis and treatment of rhabdomylysis, determination of prognosis and prevention form renal failure.

Materials and methods

Current study was a descriptive cross-sectional study. Studied subjects were selected among hospitalized patients with all cause poisoning who admitted in toxicology ward of Sina Hospital, Tabriz, Iran, during one year(2011-2012). Sample size was determined as 400 patients via statistical methods.

All data were derived from the patients' medical records, recorded in designed questionnaires and analyzed via SPSS 16. Derived data were as fallows: age, gender, medications, clinical signs and symptoms on admission and during hospitalization such as: decreased level of consciousness, seizure, agitation, fever, myalgia, fatigue, laboratory data such as CPK, liver enzymes, urinalysis (U/A), kidney function tests, developing or non developing rhabdomyolysis the number of hospitalization days, complications like renal failure and patients' clinical and labobartoy status.

Data were analyzed with central indexes (mean), diffusion indexes(standard deviation), frequency of data, Chi-Square test, independent samples t-test and one sample t-test, using SPSS™ 16 software.
In this study no intervention was done and personal information remained confidential.

Result and Discussion

Among 400 studied subjects, 210(52.5%) were male and 190(47.5%) were female. Age range was between 11 to 82 years old

with the mean of 30.36±11.46 years. Most of the patients (both males and females) aged 20-29 years.

4 patients (1%) had taken acetaminophen, 35(8.8%) alcohol, 87(21.8%) benzodiazepines, 5(1.2%) betablocker, 10(2.5%) tricyclic antidepressants (TCA, 12(3%) opium, 11 (2.8%)psychiatric medications, 1 (0.2.%) nonsteroidal anti-inflammatory drugs (NSAID), 227 (56.8%) multidrug. Toxic drug was not obvious in 8 patients (2%).

188 patients (47%) were lethargic, 22(5.5%) were in stupor state, 64(16%) in light coma and 29(7.2%) in deep coma. 97 patients (24.2%) had not decreased level of consciousness. According to the medical records, 16 patients (4%) had muscle weakness, 10(2.5%) myalgia and 60 (15%) agitation.

Liver enzymes were checked in 348 patients with minimum 11, maximum 8370 and the mean of 109.79±613.499.50 patients (12.5%) had live enzymes>45, 298 patients had normal liver enzymes and in 52 patients, liver enzymes had not been checked.

Creatinine was checked in all of the participants with minimum 0.2mg/dl, maximum 8.5mg/dl and the mean of 0.838±0.5046. Creatinine in 389 patients(97.25%) was in normal range and in 11 patients was above 1.4 mg/dl.

335 patients (83.75%) didn't have myoglobinuria, 36 patients (9%)had myoglobinuria and urinalysis hadn't been performed in 29 patients(7.25%).

24 patients (6%) had CPK>1000 U/L that among them, 11 patients(2.75% of total patients) had CPK between 1000 to 50000 and 13 patients(3.25% of total patients) had CPK>5000U/L.

Among patients in this study, 4 patients died that three of them, had CPK>1000U/L and one had CPK=771U/L. Three of them, were cyanotic on arrival and all of them had been intubated and resuscitated.

Of 400 patients, 24 (6%) had CPK>1000 and among them, 5 patients(20.83%) were female and 19 patients(79.17%) were male which this difference may be due to more muscle mass in men.

No significant correlation was found between gender and elevated CPK(Pvalue=0.4). No significant relationship was reported between age and CPK level as well(P value=0.3).

The mean of CPK in these 24 patients was 6455.79±4574.97. Among 24 patients with elevated CPK level, 14 patients(58.33%) were poisoned with multidrug, 6(25%) alcohol, 3(12.5%) opium and 1(4.16%) with psychiatric medications.

There was no significant correlation between poisoning substance and elevated CPK(P value=0.3). In 24 patients with rhabdomyolysis, 3 (12.5%) had muscle weakness (Pvalue=0.4), 2(8.33%) had myalgia (Pvalue=0.4) and 7 patients(29.16%) had agitation(P value=0.4). No significant association was seen between elevated CPKA and any of these clinical signs and symptoms.

Of 24 patients, 7(29.16%) had myoglobinuria, 6(25%) did not have myoglobinuria and 11 patients had no urinalysis in their medical records. Myoglobinuria had no significant correlation with elevated CPK(P value=0.3). Of 24 patients with rhabdomyolysis, 7(29.16%) had normal liver enzymes, 15(62.5%) had liver enzymes above normal level and 2 patients didn't have liver enzymes test.

Significant correlation was reported between elevated CPK and elevated liver enzymes (P value=0.009).

Among patients with rhabdomyolysis, 4 (16.66%) had elevated creatinine with significant relationship between elevated CPK and renal failure (P value<0.05). One of the patients with renal failure underwent dialysis with creatinine=8.5.

In 2001, poisoning became the seventh cause of death and tenth cause of disease burden in some of the countries in Europe and Central Asia with low and medium economic state. In 2004 acute poisoning led to 240000 deaths worldwide. A few studies in Iran have reported drug consumption as the most common cause of poisoning in adults, which many of them (90.2%) have been on purpose. From 2003 to 2005, 5.4% of hospital admissions in teaching hospitals of Tabriz, have been due to poisoning(11-12).

Islambulchilar in his study on 1342 poisoned patients in Tabriz concluded that 5.4% of total hospital admissions are because of poisoning. In Islambuchilar et al. study, drug was the most common cause of poisoning (60.8%) with most frequency of benzodiazepines (40.31%) and then antidepressants (31.98%)(13).

In our study the most frequent drugs, were multidrug (56.8%) and then benzodiazepines (21.8%). It should be noted that the most of our multidrug were including benzodiazepines, which are accessible in our society.

Talayee et al study in 2007, defined rhabdomyolysis as CPK>975U/L. In this study, among 180 poisoned patients, 2(1.1%) had myalgia, 5(2.8%)muscle stiffness and 5(2.8%) muscle inflammation. Opium was the most common cause of rhabdomyolysis (23.3%) and other causes in order of frequency include benzodiazepines, Phenobarbital, propranolol, aluminium phosphide, alcohol and CO poisoning. Range of CPK was 12-8390U/L and 143 patients(79%) had CPK≥975U/L(2).

Izadi et al study divided CPK amount into three groups: low(250-1500U/L), moderate (1500-10000U/L) and high (>10000U/L). In their study, most of the patients (55%) were in moderate group and only 20% in high group. In these patients range of CPK was 414-74520 U/L with the mean of 7796.95±1239.76. Mortality or morbidity rate was reported 35% in low group, 29.5% in moderate group and 75% in high group. Narcotics poisoning was the most common cause of rhabdomyolysis and the highest level of CPK was reported in TCA poisoning. In this study, 3.75% of patients developed renal failure and 8.8% died (11).

Multidrug was the most common cause of rhabdomyolysis in our study (58.33%). In Talayee et al. study, opium, in Izadi et al. study, narcotics, in Islambulchilar et al. study, benzodiazepines and in Taghaddosi Nejad et. al study benzodiazepines were reported as the most common causes of rhabdomyolysis whereas Jankovic et al. reported alcohol as the most common cause of rhabdomyolysis(10). This difference may be due to accessibility of benzodiazepines, narcotics and opium in Iran. Alcohol consumption is less common in Iran as well. Simonson and Kock found myoglobin in kidney autopsy of 20% of patients who died from poisoning (18). Welte et al. found myoglobin in kidney autopsy of 50% of deaths from poisoning(4).

Prevalence of myoglobinuria in the current study was 9% because we assessed urinalysis results instead of autopsy

specimens of kidney. In Talayee et al. study the prevalence of myoglobinuria was 13% which can be due to more prevalence of rhabdomyolysis in their study(2). On the other hand, myoglobin is rapidly cleared from urine and the time of urine analysis can change the results.

2.5% of our patients had muscle pain versus 1.1% in Talayee et al. study. Mortality rate was 1% in our study, 8.8% in Izadi et al. study, 2.9% in Robert et al. study , 2.3% in Islambulchilar et al. study and 17% in Taghaddosi Nejad et al. study. Taghaddosi Nejad et al. studied on intensive care unit (ICU) patients which can explain the higher rate of mortality compared to other studies.
Results of our study showed that poisoning is more common at 20-29 years old and prevalence of poisoning is higher in men compared to women. Among studied subjects with poisoning, 2.5% had myalgia, 4% muscle weakness and 9% myoglobinuria. If we consider only patients with rhabdomyolysis, 12% had muscle weakness, 8.33%myalgia and 29.16% myoglobinuria. These results show that small percentage of patients with rhabdomyolysis developed clinical signs and great percentage of them had no clinical signs of rhabdomyolysis therefore lack of rhabdomyolysis triad doesn't rule out the diagnosis. Significant correlation was reported between increased CPK with fever, duration of hospitalization, liver enzymes and creatinine. 6% of patients developed rhabdomyolysis which 16.66% of them (2.75% of total patients) progressed to renal failure. Despite all of the treatment modalities, 1% of total patients and 12.5% of patients with rhabdomyolysis died.

Current study had limitations such as lack of all required information in the patients' records therefore complete data recording in computerized medical records is necessary.

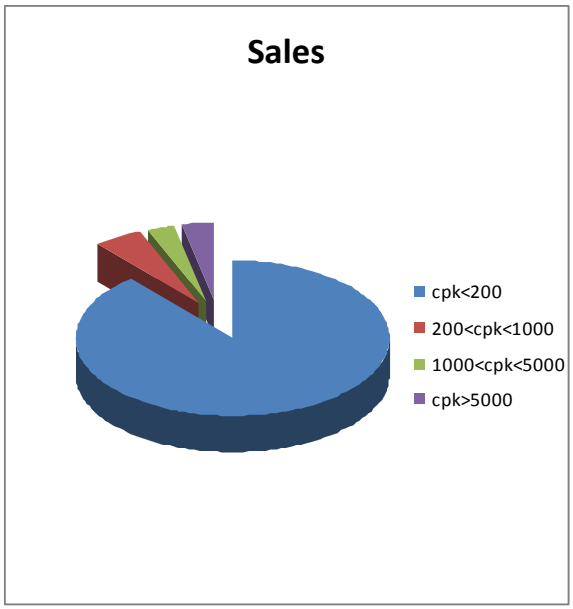

Fig.1 CPK levels in studied subjects

According to the current study and results of previous studies, poisoning is more common in young and active individuals and poisoning-induced rhabdomyolysis can lead to serious and fatal complications like renal failure. Therefore, considering high prevalence of poisoning and poisoning-induced deaths in young adults, it is necessary to pay more attention to early diagnosis and treatment of rhabdomyolysis.
Future studies on prevalence of rhabdomyolysis in different centers and regions, accurate determination of prevalence and risk factors of rhabdomyolysis, efficacy of treatment modalities and chemical and molecular assessment of poisons and correlation between toxic substance and skeletal muscle damage, are suggested.

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