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Acute Kidney Injury with Rhabdomyolysis: 25 Years Experience from a Tertiary Care Center

Rubina Naqvi*, F. Akhtar, E. Ahmed, A. Naqvi, A. Rizvi

Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan
Email: *rubinanaqvi@gmail.com

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Abstract

Objective: To describe patients presenting with acute kidney injury after rhabdomyolysis at a tertiary renal care center in Pakistan. Patients and Methods: An observational cohort of patients identified as having acute kidney injury (AKI) with rhabdomyolysis, which was diagnosed by rise in creatinine phosphokinase (CK) and lactate dehydrogenase (LDH) more than 4 times the reference range whereas AKI was defined according to RIFLE criteria. On ultrasonography, all patients had normal size non obstructed kidneys, and no other co morbid. Results: Between January1990 to December 2014, 334 patients with rhabdomyolysis and AKI registered to this hospital. Mean age was 28.22 ± 11.22 years with M:F ratio of 3.33:1. Mean values of CK and LDH were 597,749.790 ± 180,461.360 and 4077.026 ± 5050.704 U/L with reference range of 26 - 174 U/L and 91 - 180 U/L respectively. We divided the study population into 4 groups over timeline. Rhabdomyolysis etiology was divided in 3 groups; 1) traumatic, 2) non-traumatic exertional, and 3) non-traumatic non-exertional. In the last group, which spans from 2010-2014, we treated many cases with toxic rhabdomyolysis and main toxin was paraphenylenediamine (PPD). The other causes showed more or less same prevalence over two and a half decade, except non-traymatic exertional which has decreased during last 5 years without any explainable cause. Renal replacement therapy (RRT) was required on arrival in 94% cases. Complete renal recovery was observed in 70%, while 15.86% died and 10% were lost during recovery phase. A small number 2.69% left against medical advice during acute phase of illness and 0.8% developed chronic kidney disease (CKD). Conclusion: The common clinical conditions found associated with rhabdomyolysis and AKI includes trauma, immobilization, sepsis, overexertion, and drugs and toxins. In recent years, we have seen many young patients with PPD poisoning; we have found good renal recovery in patients who survived initial 2 - 3 weeks.

*Corresponding author.

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Keywords

Acute Kidney Injury, Rhabdomyolysis, RIFLE Criteria, Torture, Toxins, PPD

1. Introduction

Rhabdomyolysis is a syndrome in which muscle pain and necrosis occurs with release of intracellular muscle constituents into the circulation. A variety of events can lead to rhabdomyolysis and this result in rise of Creatinine phosphokinase (CK) levels. Presence of myoglobinuria may or may not be observed. The Symptomatology ranges from simple moderate elevations in serum muscle enzymes to life-threatening disease associated with extreme enzyme elevations, electrolyte imbalances (especially hyperkalemia), and acute kidney injury [1].

The final common pathway for injury in rhabdomyolysis is an increase in intracellular free ionized cytoplasmic and mitochondrial calcium. This may be caused by depletion of adenosine triphosphate (ATP), the cellular source of energy, and/or by direct injury and rupture of the plasma membrane [2] [3].

ATP depletion causes dysfunction of the Na/K-ATPase and Ca^{2+} ATPase pumps that are essential for maintaining the integrity of the muscle cells, resulting in release of muscle enzymes in the circulation. The exact mechanism of myoglobin causing defective glomerular filtration is not known. Previous experimental and clinical studies suggest that intra renal vasoconstriction, direct tubular injury, indirect (ischemic) tubular injury and intra luminal blockade with myoglobin casts all can play a role [4].

New classification of causes of rhabdomyolysis categorizes broadly into three groups, that is: traumatic, non-traumatic exertional and non-traumatic non-exertional. Traumatic includes crush syndrome or prolonged immobilization. Non-traumatic exertional includes marked exertion in untrained individuals, recurrent convulsions, human stampede, hyperthermia, or metabolic myopathies. While non-traumatic non-exertional mainly drugs, toxins and infections [5]-[9].

Detailed history and clinical examination often provide a clue for the cause in an individual.

Many large series have been published in the past, reporting relative frequencies of different etiologies [4] [5] [10]. In the present study, we report AKI secondary to rhabdomyolysis from single tertiary care center, over a period of 25 years.

2. Methods and Patients

An observational cohort of patients identified as having AKI, which was defined according to RIFLE criteria [11], with normal size, non-obstructed kidneys, after rhabdomyolysis, which was defined as rise in CK and lactate dehydrogenase (LDH) more than 4 times the reference range. Study includes all patients with AKI secondary to rhabdomyolysis registered at this institution from January 1990 to December 2014.

For our laboratory, reference ranges for CK and LDH are 26 - 174 and 91 - 180 U/L respectively. All biochemical tests were done on Unicel DxC 800 Synchron Clinical System, Beckman Coulter auto-analyzer.

Myoglobinuria was checked with $(NH_4)_2 \cdot SO_4$ method and markers for myoglobin were checked on pigment casts of histological samples. Renal biopsy was performed in 12 patients where history was dubious and patients reached late. For immunohistochemistry, tissue sections were immersed in peroxidase quenching solution and rinsed with PBS. Primary antibody (polyclonal rabbit anti human Myoglobin, Dako, Glostrup, Denmark) in dilution of 1:400 was applied for 30 - 60 minutes at room temperature followed by PBS rinsing. Secondary antibody (HRP: horse reddish peroxidase. Dako LSAB +/HRP kit, Dako, Glostrup, Denmark) was applied for 10 minutes at room temperature followed by PBS rinsing. Enzyme conjugate was applied for 10 minutes at room temperature followed by PBS rinsing. Chromogen substance (DAB, Dako, Glostrup, Denmark) was applied for 5 - 10 minutes followed by PBS rinsing and light counter stain with Hematoxylin and mounting of slides. The slides were visualized under the light microscope.

The patients who remained on follow up; which expands from first discharge to maximum of 23 years, and not recovered normal renal functions but remain dialysis free were labeled as CKD.

We divided the population in 4 time periods, for observing any change in trends in different causes of rhabdomyolysis. Whereas, rhabdomyolysis was divided in 3 groups based on etiology: Traumatic, which include crush syndrome and prolonged immobilization, torture causing blunt trauma, burn, and electrocution; non-

traumatic exertional include prolonged exercises by untrained personnel and prolonged convulsions, whereas; non-traumatic non-exertional include drugs, toxins, and infections. Quantitative variables reported as means ± STD and Qualitative as percentages.

3. Results

A total of 5623 patients with AKI brought to this hospital between January 1990 to December 2014, of these 334 (5.9%) were secondary to rhabdomyolysis. Average age of patients in this group was 28.22 ± 11.29 years, 258 were male and 76 were females.

Traumatic rhabdomyolysis include 28 patients from road traffic accidents, 24 from crush injury (earthquake, collapsed roof and fire arm injuries), prolonged immobilization, electrocution, blunt trauma, burn and 58 cases of torture. Last group includes person beaten up by batons, fists, leather belts, hanging upside down and sits ups given for torture purpose (**Table 1**).

Non traumatic exertional group includes 30 people with prolonged exercise in untrained people, especially in hot weather and 23 epileptic patients brought after status epilepticus (**Table 1**).

Non traumatic non exertional group include infections and poisonings with drugs, substances or venom (**Table 1**).

During different time periods that is initial 10 years, then 5 years, 5 years and 5 years, prevalence of traumatic rhabdomyolysis remains unchanged, non traumatic exertional shown decline during last 5 years, while the last group of non traumatic non exertional rhabdomyolysis has shown dramatic increase of PPD poisoning during last 5 years (**Table 2**).

The main demographic, clinical and laboratory parameters of the study population are given in **Table 3**. Majority patients were young; males were 3.3 times more than females. Majority was in advanced uremia and muscle enzymes were many folds higher than reference range (**Table 3**).

Renal biopsy was done in 12 cases and revealed acute tubular necrosis in all with presence of pigment casts in tubular lumina in 8 cases. Immunohistochemistry for myoglobin was positive in these patients.

The complete recovery from AKI was seen in 70% of patients, highest observed in non-traumatic exertional rhabdomyolysis (83%). Mortality was high in traumatic rhabdomyolysis (22.22%), among these crush injury

Table 1. Causes of rhabdomyolysis (N = 334).

Traumatic = 126	Non Traumatic exertional = 53	Non traumatic, non-exertional = 155
RTA = 28		Poison PPD = 75
Crush injury = 24 (Including fire arm injury = 11)	Prolonged exercise = 30	Alcohol binge = 10 Marihuana Binge = 9
Prolonged immobilization = 3	Recurrent Convulsions = 23	Infections = 35
Electrocution = 3		Scorpion venom = 5 Snake venom = 5
Burn = 1		Drugs over dosage = 4
Blunt trauma = 9		Others = 12
Torture* = 58		

*Torture cases include beaten up by batons, fists, leather belts, hanging upside down, sit-ups.

Table 2. Pattern over different time periods.

Cause of Rhabdomyolysis	1990-1999 (n = 67)	2000 - 2004 (n=35)	2005-2009 (n = 52)	2010-2014 (n = 180)	Total 25 yrs (n = 334)
Traumatic	42 (62)	20 (57)	32 (62)	32 (18)	126 (37.72)
Non-traumatic exertional	21 (31)	10 (28)	13 (52)	9 (5)	53 (15.86)
Non-traumatic non-exertional	4 (6)	5 (14)	7 (13)	139 (77)	155 (46.40)

*% in parenthesis.

was worst which revealed 45.83% mortality as subgroup. For non-traumatic non-exertional group, overall mortality was 12.9% with infection contributing most (14.28%). The poisoning with PPD, which comprises largest of this last group, showed mortality of 6.6% (**Table 4**). Fifty three patients died during acute phase of illness, 26 of these within 24 hours of reaching to hospital. Multi organ failure, sepsis and recurrent hyperkalemia were main causes of mortality in the study population (**Table 5**).

Table 3. Demography and laboratory values (N = 334).

M:F	3.3:1
Age mean ± SD, years	28.221 ± 11.299
Duration of insult mean ± SD, days	7.346 ± 5.510
Hb mean ± SD, g/dl	11.300 ± 2.496
Blood Urea mean ± SD, mg/l	265.895 ± 109.411
Serum Creatinine mean ± SD, mg/l	12.142 ± 5.550
LDH mean ± SD, U/l	4077.026 ± 5050.704
CK mean ± SD, U/l	59,774.790 ± 180,461.356
AST mean ± SD, U/l	1954.298 ± 2397. 769
ALT mean ± SD, U/l	888.95 ± 1100.987

Table 4. Outcome in different groups (N = 334).

Cause	Complete recovery	Partial recovery**	LAMA*	ESRF	Died
Traumatic = 126	**=84**	**=10**	**=04**		**=28**
• RTA = 28	**15**	**3**	**0**		**10**
• Crush injury = 24	**10**	**2**	**1**		**11**
• Prolonged immobilization = 3	**3**	**0**			**0**
• Electrocution = 3	**1**	**1**			**1**
• Burn = 1	**1**	**0**			**0**
• Other trauma = 9	**6**	**0**			**3**
• Torture = 58	**48**	**4**	**3**		**3**
Non traumatic Exertional = 53	**=44**	**=02**	**=00**	**=01**	**=06**
• Prolonged exercise = 30	**28**	**1**	**0**	**0**	**1**
• Recurrent convulsion = 23	**16**	**1**	**0**	**1**	**5**
Non traumatic non exertional = 155	**=107**	**=22**	**=05**	**=10**	**=20**
• Poison PPD = 75	**65**	**3**	**2**	**0**	**5**
• Alcohol binge = 10	**4**	**5**	**0**	**0**	**1**
• Marihuana binge = 9	**2**	**5**	**0**	**1**	**2**
• Infections = 35	**21**	**5**	**3**	**0**	**5**
• Scorpion bite = 5	**5**	**0**	**0**	**0**	**0**
• Snake bite = 5	**5**	**0**	**0**	**0**	**0**
• Drug over dose = 4	**3**	**1**	**0**	**0**	**0**
• Others = 12	**2**	**3**	**0**		**7**

*LAMA: refused treatment and left against medical advice, **Partial recovery: trends were towards improvement but didn't turn up for follow up.

Table 5. Cause of death (N = 53).

Cause	No.	%
MOF*	**17**	**32.07**
Sepsis	**29**	**54.71**
Hyperkalemia	**6**	**11.32**
G I bleed	**1**	**1.88**

*Respiratory, circulatory and coagulation along with AKI. 26/53 deaths occurred within first 24 hours of reaching this hospital.

4. Discussion

Rhabdomyolysis has been described for thousands and thousands of years. Old Testament describes rhabdomyolysis in Israelites who consumed quail fed on hemlock [12]. Hemlock poison, also famous to execute Socrates, can cause rhabdomyolysis and acute tubular necrosis (ATN) along with other neurologic symptoms. During spring season, birds consume large amount of buds from plant and when eaten up by humans, toxins disintegrate and cause harm [13].

Musculoskeletal trauma, in particular crush syndrome, accounts for a large proportion of the cases of rhabdomyolysis. Initial reports are from 1908 during Sicilian earthquake in Messina where rescuers searched through the rubble for weeks, and whole families were still being pulled out alive, and later in timeline from German military literature and during the bombing of London in Second World War. Pigmented casts were found in the renal tubules at autopsy; however, at that time pathogenesis was unclear [14] [15].

Additional cases were described during the Korean War [16]. The decreased incidence of posttraumatic AKI during the Vietnam War could be explained on the basis of the faster evacuation techniques and improved fluid resuscitation of affected people [17].

According to previously published studies about 10% - 50% of patients with rhabdomyolysis develop AKI [18]. Whereas with extensive traumatic injuries figure rises up to 85%. Mortality for such patients, *i.e*. severe trauma, rhabdomyolysis and AKI, has been reported up to 20% [19], more so with multi-organ dysfunction syndrome [20].

Rhabdomyolysis and crush syndrome are common results of natural disasters such as earthquakes. Many reports have been published on survivors of earthquakes who suffered from crush injury and AKI [21] [22]. In the present cohort, 10 patients were from earthquake of 2005 in northern area of country [23].

Rhabdomyolysis may complicate a high-voltage electrical injury and lightning strikes. It has been reported in 10% of subjects that survive an electrical shock. The clinical course following an electrical burn is similar to that of a crush injury. Pathogenesis can be ascribed to the electrical disruption of sarcolemmal membranes, with loss of barrier function and massive calcium influx [24] [25].

Non-traumatic myoglobinuria with AKI is a relatively common disease easy to diagnose and has an excellent prognosis [26]. Risk factors for non-traumatic rhabdomyolysis, include malignant hyperpyrexia, malignant neuroleptic syndrome, extreme exertion, recurrent seizures, bacterial and viral infections, use of certain medications, and exercise by untrained personnel especially in hot and humid weather [27]. In our study, we found 15.86% patients with history of prolonged exercise or recurrent convulsions, while 10.47% had infection, and another 27.24% were affected by different toxins. To our surprise number of patients developing rhabdomyolysis after prolonged exercise has markedly decreased during last five years of study for which we have no proper explanation.

Myoglobinuria can be estimated by chemical methods, spectrophotometry and immunologic (radial immunodiffusion, complement fixation, counter immunoelectrophoresis) methods in laboratory [28]. Most simple, "side-room" method, is to collect 5 ml of urine, mix well with 2.8 gm of $(NH_4)_2 \cdot SO_4$, allow to stand for 5 minutes and then filter, colored supernatant indicates myoglobinuria while colored precipitate hemoglobinuria [27]. Important to mention is the fact that absence of myoglobinuria does not exclude the diagnosis [5].

Non-traumatic rhabdomyolysis has also been reported with alcohol intake, where the cause is not fully understood. The patho-physiology can be quite different between short- and long-term alcohol abuses [29]. Under short-term alcohol intoxication, immobilization or coma induced by ethanol-related central nervous system sedation plays an important role in developing rhabdomyolysis. It causes muscle compression and ischemia, which will accelerate short-term alcohol myotoxicity [30], resulting in a massive breakdown of skeletal muscle over a short period of time.

In long-term alcohol abuse, electrolyte abnormalities (*i.e*., hypokalemia, hypophosphatemia, or hypomagnesaemia) may play significant causative roles for developing rhabdomyolysis [29] [31].

There is a long list of medications and recreational drugs that can cause rhabdomyolysis by different mechanisms. Any drug that directly or indirectly impairs the production or use of ATP by skeletal muscle, or increases energy requirements that exceed the rate of ATP production, can cause rhabdomyolysis [32].

Heavy metals, insects venoms and snake venom (especially Sea-Snake and Elapids), have been reported to cause rhabdomyolysis [33]-[36]. Scorpion venom has rarely been reported as direct nephrotoxic agent [37] but extensive muscle necrosis at the site of sting which was observed in our studied population as well as reported

previously, can give rise to muscle damage severe enough to cause tubular injury with myoglobin. Hemolytic uremic syndrome (HUS) has been reported after scorpion sting as a single case report in literature. [38] [39]

Another toxin, paraphenylenediamine (PPD) has been described as a hair dye since the end of 19th century. Up till now, it is reported to be used in more than 1000 oxidative hair-dyes in the USA [40] [41]. PPD is also used in the photographic or rubber industries. In addition, in many African countries, PPD in its pure form or in combination with other natural coloring extracts like Henna, is used for coloring of palms and soles for cosmetic reasons [42] [43]. Unfortunately, there are also vast numbers of unintended and intended incidents of severe to life threatening intoxication involving this synthetic compound [43] [44]. PPD intoxication leads to a severe clinical syndrome including laryngeal edema, rhabdomyolysis and subsequent renal failure, neurotoxicity and acute toxic hepatitis which *per se* can lead to dark colored urine [44]. In our experience, we have started registering the rhabdomyolysis after intoxication with PPD mainly over last two years, though reports from India and Africa as case reports or case series are there in literature [44]-[46]. In the present study, majority were young females and ingested it as an attempt for committing suicide, as the substance is easily available widely at a low cost. A case series published from India reported complete renal recovery in 61.35% of patients with PPD intoxication, but patient population was small with total cases of 13 in this particular study [44]. In our observation complete renal recovery was seen in 86.66% of PPD intoxication patients Rhabdomyolysis in association with crush injury has been reported with poor prognosis about seven decades ago [15], but with passage of time as understanding of patho-physiology improved and early methods of resuscitation adopted in large catastrophic situations, mortality rate has declined [22]. In the present study, mortality was 46% in crush injury victims but half of these succumbed to death within 24 hours of arrival to this hospital, indicating extent of insult and delay in reaching to this particular tertiary care service and poor infra structure of health facilities in country.

5. Conclusion

This study was conducted over a span of two and a half decades; we have observed changes in the pattern of causes of rhabdomyolysis. During the first decade, torture and blunt trauma was more common while during last five years largest contributing factor was toxic rhabdomyolysis with PPD ingestion. Patients who survived initial period of insult show good renal recovery. Mortality is mostly contributed by multi organ failure and sepsis. Remarkable number of deaths occurred soon after arrival highlighting the need of good supportive, well equipped infra structure at national level.

Conflict of Interest

None.

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