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Acute Kidney Injury Following Crush Injury and Earthquakes.

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Abstract:

Earthquakes may provoke crush injuries complicated by acute kidney injury (AKI). Management of rhabdomyolysis and acute renal failure (ARF) following crush injury is through improve the setting of primary triage and intensive care unit (ICU). This article summarizes scientific reports on management strategies of the ARF following crush injury available until 2010. Measures that should take into account for disasters and traumatic rhabdomyolysis include establishment of epidemiologic data about specific disaster conditions that predispose traumatic rhabdomyolysis and AKI, assessment and rescue team, local and public interventions, and programmed medical and social trained team. Early rehydration, urine alkalinization and, forced diuresis improve the outcome of kidney injury, risk of permanent renal failure and mortality.

Keywords: Rhabdomyolysis, Acute kidney injury, Earthquake

Introduction:

Sudden-impact natural disasters such as earthquakes present a serious challenge to medical personnel in both developed and less developed countries. Crush syndrome with acute renal failure has been identified as a major medical complication that occurs among people whose limbs are trapped by heavy objects during natural disasters such as earthquakes or volcanic eruptions. Rescue and field medical teams should be trained to rec-

ognize and promptly treat the problems associated with prolonged limb compression and should carry the appropriate fluids and medications to treat the complications of traumatic rhabdomyolysis.[1]

Rhabdomyolysis — literally, the dissolution of striped (skeletal) muscle — is characterized by the leakage of muscle-cell contents, including electrolytes, myoglobin, and other sarcoplasmic proteins (e.g., creatine kinase, aldolase, lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase) into the circulation. Massive necrosis, which is manifested as limb weakness, myalgia, swelling, and gross pigmenturia without hematuria, is the common denominator of both traumatic and non-traumatic rhabdomyolysis.[2,3]

Recent experiences of large earthquakes have highlighted the important role of nephrologists in the recovery of regular dialysis therapy and management of crush syndrome. Early establishment of intra- and inter-hospital domestic and international networks seems to be mandatory for the achievement of more organized activities in disaster relief.[4] In this manuscript, approach and management of acute kidney injury following crush injury for improving medical strategy planning, and response to casualties that cause acute renal failure is summarized.

Methods:

A review of literature was performed in 2010 to summarize scientific reports on rhabdomyolysis and acute renal failure in Iran and other countries. Articles indexed in the PubMed database and Google for medical journals. Papers published during recent years (1986-2010) were searched by using the following key words: rhabdomyolysis, acute renal failure, crush injury, and earthquake.

Epidemiology of rhabdomyolysis following crush injury, earthquakes:

Common causes of rhabdomyolysis include: trauma, seizures, strenuous exercise, heat stroke, electrolyte disorders as hypokalemia, hypophosphatemia, genetic defects in muscle metabolism, and drugs such as illicit drugs, and lipid-lowering agents.[2, 3] Earthquakes threaten large sections of the globe, and sometimes densely inhabited areas, such as the Mediterranean, Middle and South-East Asia and California. Major cities, like Istanbul, Tehran and San Francisco, are located in high risk zones. On 6 April 2009, an earthquake struck the city of L□Aquila and the surrounding Abruzzo Mountains. The disaster left 66 000 people homeless, while 1500 were wounded and 298 died. Although Europe as a whole is not so often affected by massive earthquakes, Italy is an exception with 12 earthquakes with an intensity >6.0 on the Richter scale during the last 100 years.[5, 6, 7]

The 1990 lran earthquake affected two provinces with a population of 2.3 million, resulting in at least 13888 deaths and 43390 injured, and in 33615 hospitalizations. Acute renal failure (ARF) requiring dialysis support was diagnosed in 156 patients nationwide, with a mortality rate of 14%. Three teaching hospitals of the Tehran University of Medical Sciences admitted 495 patients, with overall mortality of 7.5%. Of these, 30 (6%) required dialysis support, with mortality of

40%, accounting for one-third of all deaths. On admission, patients with ARF were more severely injured, with significantly higher incidence of multiple trauma, peripheral nerve damage, elevated plasma concentrations of muscle enzymes, potassium and phosphate, and abnormal urinalysis. In one of the three hospitals, patients were treated with a standardized hydration protocol coupled with a cautious approach to fasciotomy. The incidence of ARF, mortality associated with ARF, and fasciotomy were lower in this group.[8]

On December 26, 2003, an earthquake measuring 6.51 on the Richter scale struck the city of Bam in the Kerman Province in southeastern Iran. Of 801 patients that transferred to Shiraz hospitals: total mortality was 21 (2.6%) and acute renal failure mortality was 3 (15%). There was a positive correlation between time spent under rubble and peak serum creatine phosphokinase(CPK) level ($p = 0.035$), acute renal failure duration ($p = 0.047$), and admission potassium levels ($p = 0.033$). Serum CPK level was positively correlated with acute renal failure duration ($p = 0.008$). Patients who had received standard treatment had significantly shorter duration of acute renal failure (7.1 versus 9.4 days, $p = 0.008$) and less need for dialysis (1 versus 6, $p = 0.007$) than patients who were treated variably.[9]

A front-line intensive care unit (ICU) was set up in a tent after the disastrous Wenchuan earthquake (May, 12, 2008, China). Eighteen of the 32 crush injury patients developed traumatic shock, 9 had acute renal failure, 6 had acute heart failure, 2 had stress ulcers and 4 had multiple organ dysfunction syndrome (MODS). The limb distension and sensory dysfunction were improved and the urine output was increased or even restored to the normal level in some patients. Five (15.63%) patients underwent amputation due to severe infection in our group. Establishment of a well-equipped front-line ICU close to the epicenter of the earthquake allows for prompt on the spot rescue of critical patients with crush injury, greatly decreasing the mortality rate and complications and avoiding amputation.(10) Data of 146 patients in Wenchuan earthquake with spinal injuries of Wenchuan earthquake showed the major types of spinal fracture are compression fracture and burst fracture, and the occurrence rates of spinal injury, combined injury and multilevel vertebral body injury were high.(11) A review of 215 multidetector chest computed tomographic (CT) scans of 215 patients who sustained crush thoracic injuries in the Sichuan earthquake at May 12, 2008 showed crush thoracic trauma was a life-threatening injury and has the potential for multiple fractures and pulmonary parenchymal injuries.[12] A retrospective review was conducted of medical records of 6107 patients hospitalized during the first 15 days after the earthquake, collected from 48 affected hospitals in the disaster area and 47 backup hospitals in the surrounding area from 1995 catastrophic Hanshin-Awaji earthquake. The results suggest that the existing emergency medical service system was not adequate for this urban earthquake. The study announces the need for improved communications between hospitals, a well equipped patient transport system,

and a well coordinated disaster response mechanism.[13]

In Japan, there are nearly 1000 earthquakes per year that can be felt, and more than 15 earthquakes are greater than magnitude 6.0. Accordingly, Japan is socially prepared; social frameworks including buildings and transport facilities have been designed and constructed with sufficient strength for this magnitude of earthquake.[14]

During catastrophic earthquakes, crush syndrome is the second most frequent cause of death after the direct impact of trauma. The Marmara earthquake, which struck Northwestern Turkey in August 1999, was characterized by 639 crush syndrome victims with acute renal problems. Overall mortality rate was 15.2%.[15] There were 639 renal victims of the Marmara earthquake occurred on 1999, of whom 477 needed some form of renal replacement therapy. In a multivariate model, sepsis was associated with increased mortality ($p = 0.0002$, odds ratio 2.45, 95% confidence interval 1.52-3.96). 53 (8.2%) and 41 (6.4%) patients had wound and pulmonary infections, respectively. Most of the infections were nosocomial in origin and caused by Gram-negative aerobic bacteria and Staphylococcus spp. Infectious complications are common in renal victims of catastrophic earthquakes and are associated with increased mortality when complicated by sepsis.[16] The cumulative incidence of treated AKI related to number of deaths or victims might differ substantially among earthquakes. Many factors may affect the frequency of AKI: hampered rescue and transport possibilities; destroyed medical facilities on the spot; availability or not of sophisticated therapeutic possibilities and structure of the buildings might all have impacted on different cumulative incidence between Kashmir and Marmara.[17]

A destructive earthquake devastated northwestern Armenia on December 7, 1988. The size of the affected area, the time of the day when it occurred, deficiencies in the design and construction of buildings, and inadequate initial rescue and relief capabilities resulted in one of the most lethal and traumatic natural disasters of the century. A large number (estimated at 225 to 385) of victims who had sustained crush injury developed myoglobinuric acute renal failure requiring dialytic support. International dialysis relief efforts resulted in meeting the immediate acute needs and provided the motivation and elements of the more efficient system for the future delivery of maintenance dialysis.[18]

Pathophysiology and manifestations of rhabdomyolysis:

At the kidney level, the main pathophysiological events in the genesis of myoglobinuric ARF are renal vasoconstriction, intraluminal cast formation, and direct haeme-protein-induced cytotoxicity. Myoglobin is easily filtered through the glomerular basement membrane and passes into the tubules. When water is progressively reabsorbed from tubular fluid, the concentration of myoglobin rises until it precipitates, causing obstructive cast formation. Likewise, the high rate of uric acid generation and excretion may additionally contribute to tubular obstruction. These processes leading to obstruction are aggravated by

renal vasoconstriction and a decreased glomerular perfusion pressure. They result from intravascular hypovolaemia caused by uptake of water by the damaged muscles. It is not uncommon for more than 10 litres of fluid to accumulate in the damaged limbs. The fall in glomerular filtration decreases urinary flow and enhances tubular water reabsorption. Another factor in the precipitation of myoglobin and uric acid is a low pH in tubular urine. When pH decreases, the solubility of myoglobin is progressively lost.[19, 20] Patients with acute rhabdomyolysis usually present with pigmented granular casts, reddish-brown urine supernatant, and markedly raised serum creatine kinase. There is no defined threshold value of serum creatine kinase above which the risk of acute kidney injury is markedly increased.[21] The risk of acute kidney injury in rhabdomyolysis is usually low when creatine kinase levels at admission are less than 15,000 to 20,000 U per liter. Although acute kidney injury may be associated with creatine kinase values as low as 5000 U per liter, this usually occurs when coexisting conditions such as sepsis, dehydration, and acidosis are present.[21, 22, 23] Under physiological conditions, the plasma concentration of myoglobin is very low (0 to 0.003 mg per dl). If more than 100 g of skeletal muscle is damaged, the circulating myoglobin levels exceed the protein-binding capacity of the plasma and can precipitate in the glomerular filtrate. Excess myoglobin may thus cause renal tubular obstruction, direct nephrotoxicity, and acute renal failure.[24] Myoglobinuria can be inferred if urinary dipstick testing shows a positive result for blood when there are no red cells in the sediment. This false positive result for blood occurs because the dipstick test is unable to distinguish between myoglobin and hemoglobin. The test has a sensitivity of 80% for the detection of rhabdomyolysis.[21, 25] Serum myoglobin levels peak well before serum creatine kinase levels, and the peak value for blood myoglobin might be a good predictor of rhabdomyolysis-induced ARF.[26]

Acute kidney injury associated with rhabdomyolysis often leads to a more rapid increase in plasma creatinine than do other forms of acute kidney injury. However, this finding may reflect the overrepresentation of young, muscular men among patients with rhabdomyolysis rather than increased creatinine or creatine release from injured muscle.[21, 27, 28, 29] Another characteristic feature of rhabdomyolysis-induced acute kidney injury that is different from the manifestation of other forms of acute tubular necrosis is the frequent, but not universal, presence of a low fractional excretion of sodium (<1%), perhaps reflecting the primacy of preglomerular vasoconstriction and tubular occlusion rather than tubular necrosis.[21, 30] The electrolyte abnormalities that can occur with rhabdomyolysis include hyperkalemia (which can be rapidly increasing), hyperphosphatemia, hyperuricemia, high anion-gap metabolic acidosis, and hypermagnesemia mainly when renal failure is present. Hyperkalemia is an early manifestation of rhabdomyolysis, and serum potassium can occasionally reach life-threatening levels both in patients with severe traumatic rhabdomyolysis and in those with nontraumatic rhabdomyoly-

sis.[21, 31, 32] Hyperuricemia is also usually present owing to the liberation of nucleosides from injured muscle and can contribute to renal tubule obstruction since uric acid is insoluble and may precipitate in acidic urine. Hypocalcemia is a common complication of rhabdomyolysis and usually results from calcium entering the ischemic and damaged muscle cells and from the precipitation of calcium phosphate with calcification in necrotic muscle. Hypercalcemia associated with recovery of renal function is unique to rhabdomyolysis-induced acute kidney injury and results from the mobilization of calcium that was previously deposited in muscle, the normalization of hyperphosphatemia, and an increase in calcitriol.[21, 33]

Treatment:

Early fluid resuscitation (within the first six hours, preferably before the victim is extricated) is essential. The preferred fluid is isotonic saline, given at a rate of 1 liter per hour (10 to 15 ml per kilogram of body weight per hour), while the victim is under the rubble, followed by hypotonic saline soon after rescue. Adding 50 mEq of sodium bicarbonate to each second or third liter of hypotonic saline (usually a total of 200 to 300 mEq the first day) will maintain urinary pH above 6.5 and prevent intratubular deposition of myoglobin and uric acid.[34, 35] If urinary flow exceeds 20 ml per hour, 50 ml of 20 percent mannitol (1 to 2 g per kilogram per day [total, 120 g] [34, 36], given at a rate of 5 g per hour) may be added to each liter of infusate. The addition of mannitol also decreases compartmental pressure.[34, 37]

Once a patient with the crush syndrome has been hospitalized, urinary output should ideally exceed 300 ml per hour. Such a goal may require the intravenous infusion of up to 12 liters of fluid per day (4 to 6 liters of which will contain bicarbonate). The volume administered is generally much greater than the urinary output; the difference between intake and output is due to the accumulation of fluid in the damaged muscles, which may exceed 4 liters. This protocol should be continued until clinical or biochemical evidence of myoglobinuria disappears (usually by day 3). However, the urinary response may differ from patient to patient, and fluid administration should be individualized according to the patient's clinical course [34, 38], or central venous pressure measurements, with the latter approach considered optimal. If the patient cannot be monitored closely because of chaotic disaster conditions, less than 6 liters of a mannitol–alkaline solution should be infused per day to avoid volume overload.[34, 20] Hypocalcemia should be treated only if it is symptomatic, because early intramuscular accumulation of calcium is followed by hypercalcemia at later stages.[20] Patients with insufficient urinary output should be monitored closely, so that hypervolemia can be prevented or, if necessary, dialysis initiated. Serum potassium levels should be measured at least three or four times daily, especially in the first days after a patient is admitted and in patients with severe trauma, who are at higher risk for hyperkalemia than are patients with less severe injuries.[34, 39] Patients with rhabdomyolysis that is associated with acute kidney injury usually present

with a clinical picture of volume depletion that is due to the sequestration of water in injured muscles. Therefore, the main step in managing the condition remains the early, aggressive repletion of fluids; patients often require about 10 liters of fluid per day.[21, 40] It is known that precipitation of the Tamm–Horsfall protein–myoglobin complex is increased in acidic urine.[21, 41] Aalkalinization inhibits reduction–oxidation (redox) cycling of myoglobin and lipid peroxidation in rhabdomyolysis, thus ameliorating tubule injury.[21, 42] It has been shown that metmyoglobin induces vasoconstriction only in an acidic medium in the isolated perfused kidney.[21, 43] Aspartate aminotransferase (AST) concentrations decrease in parallel to CPK, suggesting skeletal muscle may be a significant source of AST elevation in these patients.[44] Whatever the real, consistent benefits of urine alkalinization in patients with rhabdomyolysis, there is evidence that massive infusion of normal saline alone can contribute to metabolic acidosis, mainly owing to the dilution of serum bicarbonate with a solution relatively high in chloride ions, generating hyperchloremic metabolic acidosis with observed reductions in serum pH of as much as 0.30 units.[21, 45] Therefore, administration of both normal saline and sodium bicarbonate seems to be a reasonable approach when fluid is being replenished in patients with rhabdomyolysis, especially patients with metabolic acidosis. If sodium bicarbonate is used, urine pH and serum bicarbonate, calcium, and potassium levels should be monitored, and if the urine pH does not rise after 4 to 6 hours of treatment or if symptomatic hypocalcemia develops, alkalinization should be discontinued and hydration continued with normal saline. The use of diuretics remains controversial, but it is clear that it should be restricted to patients in whom the fluid repletion has been achieved. Mannitol may have several benefits: as an osmotic diuretic, it increases urinary flow and the flushing of nephrotoxic agents through the renal tubules; as an osmotic agent, it creates a gradient that extracts fluid that has accumulated in injured muscles and thus improves hypovolemia; finally, it is a free-radical scavenger.[21, 46, 47] Most data on the action of mannitol come from studies in animals, which collectively show that the protective effect of mannitol may be attributable to its osmotic diuretic action rather than to the other mechanisms.[21, 48] Mannitol should only be given after volume replacement and avoided in patients with oliguria. A 20% mannitol infusion at a dose of 0.5 g/kg is given over a 15-minute period and subsequently followed by an infusion at 0.1 g/kg/h. Adjustments are made to maintain urine output at >200 ml/h. Urinary and serum pH levels are monitored, with acetazolamide added if the serum pH is >7.45 or urinary pH remains <6.0.[49, 50]

In addition, high accumulated doses of mannitol (>200 g per day or accumulated doses of >800 g) have been associated with acute kidney injury due to renal vasoconstriction and tubular toxicity, a condition known as osmotic nephrosis. During the time mannitol is being administered, plasma osmolality and the osmolal gap (i.e., the difference between the measured and calculated serum osmolality) should be monitored frequently

and therapy discontinued if adequate diuresis is not achieved or if the osmolal gap rises above 55 mOsm per kilogram.[21, 51] Loop diuretics also increase urinary flow and may decrease the risk of myoglobin precipitation, but no study has shown a clear benefit in patients with rhabdomyolysis. Therefore, loop diuretics in rhabdomyolysis-induced acute kidney injury should be used in the same manner as that recommended in acute kidney injury that is due to other causes.[21, 52, 53] The electrolyte abnormalities associated with rhabdomyolysis-induced acute kidney injury must be treated promptly; the correction of hyperkalemia, which occurs very early in the course of the disease, is especially important.[21, 54] Agents that cause a shift of potassium from the extracellular to the intracellular space (e.g., hypertonic glucose and bicarbonate) are effective only temporarily, and the only means of removing potassium from the body is diuresis (effective kaliuresis), the use of intestinal potassium binders, or dialysis. In contrast, early hypocalcemia should not be treated unless it is symptomatic or unless severe hyperkalemia is present. Calcium-containing chelators should be used with caution to treat hyperphosphatemia, since the calcium load could increase the precipitation of calcium phosphate in injured muscle.

When acute kidney injury is severe enough to produce refractory hyperkalemia, acidosis, or volume overload, renal-replacement therapy is indicated, principally with intermittent hemodialysis, which can correct electrolyte abnormalities rapidly and efficiently.[21,39,31,55]

Conclusion:

Disasters cause significant morbidity and mortality; the post-disaster period is characterized by confusion and chaos, which further contribute to the death toll. The crush syndrome is the second most frequent cause of mortality after direct impact of trauma. Renal disaster crush victims have complex pathologies and need extensive and expert health care. Also chronic dialysis patients need continued support and care; if maintenance dialysis cannot be offered for a critical period, death becomes inevitable.[56] Therefore, in disaster-prone countries, preparations for the management of renal patients should begin before disaster, and include three stages: Composing of the disaster response team; organizing educational activities that target public, rescue teams, non-nephrological and nephrological para- medical personnel as well as chronic dialysis patients; advance planning of personnel, material and dialysis services. In the aftermath of the disaster, both external and local interventions should act synergistically to apply an 'action plan', which comprises a series of actions aiming at the provision of an effective disaster response. These steps may provide an effective health care and the highest chance of survival to the unfortunate renal disaster victims.[56] Rhabdomyolysis is associated with infectious diseases in approximately 5% of cases and acute kidney injury occurs in 33-50% of cases. Acute kidney injury due to rhabdomyolysis should be considered as a possible complication of gangrenous myositis.[57]

Expected deficits faced in earthquakes are: injured subjects and homeless fami-

lies, desrtruction of medical facilities, insufficient medical supplies, disturbed telephone networks, fundamental supplies of water, gas and electricities, and main roots. Measures that should take into account in areas with high rates of natural disasters and traumatic rabdomyolysis before and after occurrence of disaster include: introducing prepared assessment, rescue team consisting of public and medical personnel, local and public interventions, programmed medical and social trained subjects to provide appropriate preventive intervention and therapeutic approach consisting of emergency/ intensivist/ nephrologists/ paramedical personnel, and material providers.

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