

Up To Date in Rhabdomyolysis: Concepts and Protocol Evaluation

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Abstract- Introduction: Rhabdomyolysis is the consequence of some diseases commonly seen in the emergency services, with several complications. In addition, there are lots of Rhabdomyolysis protocols in different countries and also in Brazil, with many points of agreement and others with divergent opinions, like the time of drugs administration and their posology. There are many variations and little evidences in the few studies and researches on humans.. **Objectives:** This paper aims to discuss the various protocols and reviews existing literature in order to adapt them to our institutional reality and the best treatment protocol. **Methods:** This study analysed protocols and updated concepts on Rhabdomyolysis. An non systematic review of protocols of all over the countries was performed. **Results:** All protocols focus on hydration and in a earlier diagnosis. Support treatments differs from service to service. **Discussion and Final Comments:** We hope that this study and research standardise the current treatment of the Rhabdomyolysis, based on evidences and clinical findings of various countries and thereby decrease the risk of it's most important complication: acute renal failure.

Index Terms- *Rhabdomyolysis; myoglobinuria; creatine phosphokinase; protocol evaluation.*

I. INTRODUCTION

Rhabdomyolysis is an acute syndrome and potentially lethal, which manifests clinically and through laboratory testing, and results from the lysis of skeletal striated muscle cells causing the release of intracellular substances into the systemic circulation, thus causing mostly damages and disturbances of renal tissue [1,2].

Approximately 26,000 cases of hospitalisation associated with rhabdomyolysis are reported every year in the United States. Rhabdomyolysis causes acute kidney injury in 13-67% of affected individuals, accounting for 5 - 10% of ARI cases in the U.S. [1]

Rhabdomyolysis aetiology is a complex and multifactorial syndrome with inherited (metabolic myopathies and muscular dystrophy) and acquired causes. Hereditary causes are uncommon and may appear in patients with recurrent episodes of muscular pain and family-related epidemiology [3].

The most common acquired causes can be divided into 3 major groups: traumatic and nontraumatic joint, the latter being a combination of causes [4].

The most frequent acquired causes are alcohol consumption, intense physical exercise, traumatic muscular compression and the use of certain pharmaceuticals and drugs [1].

Traumatic causes are related to compressive traumas (automobile accidents, earthquakes), burns and electrical injuries [4].

Non-traumatic causes are currently considered 5 times more frequent [5]. A 1982 study showed that 59% of the 87 patients presented one of the risk factors among alcohol intake, compression of soft tissues, seizures, and trauma history [3]. Another study published in 1984, identified other predisposing factors, 60% of which corresponding to trauma, ischemia and polymyositis, the remainder was associated with overdose, exercise, seizures, burns, sepsis, hereditary diseases and viruses.

A wide variety of drugs and toxins are present in approximately 80% of cases of rhabdomyolysis. Ethanol consumption, illegal drugs and statins are the most common ones [5].

Among the causes of rhabdomyolysis due to poisoning, the most common illegal drug is the use of heroin or cocaine, with about 20% cocaine overdoses being complicated with rhabdomyolysis. Statins can cause muscular pain in 10% of patients using it regularly, but cases of rhabdomyolysis reach only 0.1 to 0.2 cases per 1,000 persons / year [6,7].

The exercise-induced rhabdomyolysis is also a worrying issue. It may be due to excessive muscular exhaustion, prolonged exposure to heat, coexisting sickle-cell trait, use of dietary supplements (e.g, ephedra). In a series reported in the U.S., 57% of an ultra-marathon participants showed myoglobulinemia, but none developed ARI. In another medium studied (the military) it was demonstrated that it occurs in 2-40% of recruits during basic training.

As expected, risk factors include lack of physical conditioning and early introduction of repetitive exercises. Most cases are self-limited, there being no evidence of renal or muscular damage in the long run. It is worth noting that 25% of all cases of AMI in American military circles between 1980 and 2000 were associated with rhabdomyolysis, leading to ARF in 33% of cases [6,8].

The mechanisms involved in the pathogenesis of rhabdomyolysis are directly related to muscular cells injury. The injury causes a shift in the balance of calcium homeostasis and

the fall of Adenosine triphosphate (ATP). The decrease of ATP impairs the operation of pumps involving suitable calcium transport, thus resulting in increased sarcoplasmic calcium [6].

The excess calcium results in persistent contraction of muscle fibers, depleting energy reserves, producing free radicals, activating vasoactive molecules, releasing proteases and ultimately cell death. After the reestablishment of perfusion to the injured tissue, leukocyte migration occurs and oxygen is consumed, creating more free radicals. This mechanism establishes an inflammatory reaction that is self-perpetuating, leading to more muscular lysis and release of intracellular toxins into the systemic circulation [1,9].

The major components of the cellular content acting in the pathophysiology of renal injury are myoglobin, potassium, lactic acid, purines and phosphate. At present there are accepted three main mechanisms in kidney injury: a tubular obstruction, renal ischemia, and direct tubular injury through the toxicity of iron. Obstruction by myoglobin occurs mainly in the distal tubules. Direct injury through cytotoxicity occurs mainly in the proximal tubules, and is caused by the toxic effect of iron, which stimulates lipid peroxidation [6].

They contribute to the precipitation of myoglobin, the release of lactic acid, and nucleotides, which are metabolised in uric acid, creating an acidic environment, which facilitates the precipitation of myoglobin in renal tubules. Another mechanism of injury is renal ischemia due to imbalance between mediators of vasoconstriction and vasodilatation, especially nitric oxide and its *scavenger* effect, thus prevailing vasoconstriction and drastically decreasing renal blood flow [8,9].

The clinical presentation of rhabdomyolysis is often nonspecific and patient outcome depends on its precipitating factor. [2] Its signs and muscular symptoms are present in only 50% of cases [8], presenting muscular pain, tenderness, weakness, stiffness and fasciculations. Also, the patient present malaise, vomiting, nausea, fever and palpitations, whose most important signals are decreased urinary output and change in urine color (darker, reddish-brown) [1].

The diagnosis is made by high degree of suspicion against the clinical presentation. Therefore, considering the predisposing factors for rhabdomyolysis may help in diagnosis [2].

The change in urinary coloration is generally the first clue for the diagnosis of rhabdomyolysis, which has the heme fraction in urine [2].

The definitive diagnosis is made from laboratory tests. There is no consensus about the cutoff value of CPK (muscle creatine phosphokinase), but some considerer very probable diagnosis when higher than 1000 U/L. Is is important to note that myoglobinuria is a very important factor in diagnosis, however, has a short half life and is almost never measured and identified in laboratory tests [10].

Orthotolidine of Urine Test I: Urine dipstick test for detection of heme fraction (occurring in myoglobin), but their absence does not rule out rhabdomyolysis, due to its short half-life and the need for high serum concentration [2]. Urine I usually shows absence of hematuria.

Serum creatine phosphokinase (CPK) is released into the systemic circulation after the death of striated muscle cells, constituting an unspecific marker for rhabdomyolysis. However, persistent elevations of CPK indicate continuous muscle injuries

that may aid in diagnosis, the presence of compartment syndrome being excluded [1].

Serum and urine myoglobin: has rapid hepatic metabolism and renal excretion, thus being little sensitive. Therefore, the serum concentration of myoglobin returns to normal levels in around 1-6 hours. In plasma concentrations above 300ng/mL, it becomes detectable in urine, and its color changes in urinary concentrations above 10 0mg/dL [1].

The muscle damage causes release of phosphorus into the blood stream, changing the calcium-phosphorus ratio. Therefore, hypocalcemia and hyperphosphatemia may occur, which are generally asymptomatic and do not require treatment [2].

With progression to renal failure in these patients, creatinine rises disproportionately in relation to urea due to its release by muscle injury. Therefore, there is disproportionate elevation of urea due to catabolism of muscle proteins [2].

Other tests are also important: blood count, serum calcium, potassium, phosphorus, blood gases, coagulation, and albumin, so as to avoid complications and correct the evolutionary framework of the aforementioned rhabdomyolysis [6].

The differential diagnosis vis-à-vis the clinical presentation, includes hemoglobinuria, hematuria diseases (trauma, tumors, gallstones), acute intermittent porphyria, liver disease with dark urine and severe infections [2].

Treatment of rhabdomyolysis is still controversial, since there are few randomized controlled studies conducted in humans, making it difficult to establish a standard treatment with a high degree of evidence.

However, there is a consensus in the treatment of disease, which is based on factors that enhance prevention of acute renal insufficiency. It is important to recognise this condition early, as the correct and early treatment can prevent possible complications and allows clinical improvement. [1] Even in patients using dialysis techniques, renal function is recovered in most cases [1,2,11].

The most commonly occurring complications of rhabdomyolysis are hypocalcemia, hyperphosphatemia, hyperkalemia, hyperuricemia, compartment syndrome, peripheral neuropathy, disseminated intravascular coagulation, and renal failure. [2]

This paper aims to discuss the various protocols and reviews existing literature in order to adapt them to our institutional reality and the best treatment protocol.

II. RESEARCH ELABORATIONS (METHODS)

An non-systematic review of the medical scientific literature was performed using the database of PubMed, Lilacs, SCOPUS and by the analysis of national and international centers protocols.

Articles were researched in the english, spanish and portuguese languages, using the word "rhabdomyolysis", with no limits in the research concerning to age, date or gender, at PubMed / MEDLINE, LILACS, Scopus and SCIELO databases.

Two authors were responsible for selecting all items; all abstracts were read and from the information contained therein, if they were rhabdomyolysis articles, these were read in full way.

The articles read in full were included covering the information about aetiology, diagnosis, clinical presentation,

laboratorial tests, treatment and it is related to details, complications and other relevant points.

Both authors reviewed the inclusion of articles in the review. Review articles with no clinical informations cited above were excluded, and also those who not concern to those topics.

An statistical analysis was performed to compare groups using the Sigma XLversion 6.22 software.

The study was approved by the research ethics committee of the institution.

III. RESULTS

Through literature search it were identified 7383 articles about rhabdomyolysis, and 1023 were review articles, 139 are clinical trial, 15 controlled clinical trial, 3 guidelines, 3844 case reports, 64 editorials, 11 classical and historical articles, 114 systematic reviews and 29 meta-analysis.

The protocols of some institutions around the world are presented below and detailed for better discussion.

USP Protocol (São Paulo University , Brazil) [12].

. Treatment

The goal of the treatment is to prevent rhabdomyolysis and acute renal injury by treating predisposing conditions such as volume depletion, tubular obstruction, aciduria and the release of free radicals. The treatment can be divided into:

. Hydration

The most important treatment is to maintain an vigorous hydration with fast IV infusion, 0.5-1L bolus of saline, maintaining this system of hyper-hydration for 48-72 hours. Leading to a urinary output of at least 2mL/Kg/h (200 - 300 mL / h).

. Alkalinization

Another important topic is urine alkalinization, which must be prescribed 140mEq sodium bicarbonate in 1L of dextrose, and this infusion will depend on urinary pH, which should be kept to a value greater than 6.5. A 1mEq/kg bolus of sodium bicarbonate should also be prescribed, being careful with the alkalinization risks and especially worsening hypocalcemia.

0 Mannitol

When the patient reaches a good urinary output, it must be prescribed 10% mannitol, 15 to 45ml per hour (about 5g / h).

. Dialysis

If the treatment fails, the patient should be undergo dialysis, otherwise the clinical support should be maintained and the complications should be treated (causes of rhabdomyolysis), performing a periodic monitorization of electrolytes levels, renal function and treat the hyperkalemia.

. Complications

Hyperkalemia is common and may require aggressive treatment. Hypocalcemia in the early treatment rarely needs replacement. Other complications associated with

rhabdomyolysis are: disseminated intravascular coagulation; hypocalcemia; hyperphosphatemia (hypophosphatemia may occur lately); hyperkalemia; hyperuricemia; peripheral neuropathy and compartment syndrome.

USA Protocol [13].

The initial management of patients with established diagnosis of rhabdomyolysis has as main objective the prevention of acute kidney injury induced by myoglobin, minimising not only the hypnotic effects of low flow but also induced injury by the generation of cylinders in renal tubules. [12, 13] Thus, it is recommended that the patient should be admitted to ICU or emergency bed, properly monitored and with a well established venous access.

In the acute phase of treatment, the preservation of renal function and correction of metabolic disturbances are the main goals to be achieved. [14]

. Hydration

Vigorous fluid replacement should be performed as early as possible, always with 0.9% NaCl, avoiding solutions containing potassium so there is no worsening of hyperkalemia associated with the disease. The infusion rate should be 1.5 L / h in order to maintain urinary flow rate rate of 200-300ml / h. This overhydration plan should be maintained until it achieves serum CK levels lower than 1000IU / l. At this time, it is important that the patient is constantly evaluated for the development of heart failure or pulmonary edema, mainly.

. Alkalinization

Patients with severe cases of rhabdomyolysis (CK > 5000 IU / l) or showing increasing levels of CK despite adequate hydration volume, benefit from this approach. In addition, for the use of bicarbonate, three conditions must be met: hypocalcemia should not be present; arterial blood pH should be less than 7.5; serum bicarbonate should be less than 30mEq / L. The initial infusion should be at 130 mEq / L, with an infusion rate of 200 mL / h for urinary pH exceeds 6.5. In patients receiving bicarbonate, serum calcium levels should be measured every two hours, as well as the arterial blood pH. If the patient does not alkalize their urine after 4 hours, develop symptomatic hypocalcemia, present arterial blood pH higher than 7.5 or bicarbonate higher than 30mEq / L, one should stop the bicarbonate infusion and maintain the saline infusion.

. Mannitol

Due to the induced osmotic diuresis, mannitol is used in cases of rhabdomyolysis. [12] In severe cases, with serum CK reaching values greater than 30,000, one can consider using a dose of 1 to 2g/kg with infusion speed of 5 g / hr. This medication should be used only in patients who already have adequate urine output (> 20 mL / h) and the plasma osmolal gap and serum osmolality should be calculated. Discontinuation of the drug should be taken if diuresis suffers reduction or the osmolal gap reaches values exceeding 55mOsm/kg.

. Complications

If the measures do not show effect and the patient has excess plasma volume, hyperkalemia greater than 6.5 mEq / L, metabolic acidosis with arterial blood pH below 7.1 or signs of uremia, the hemodialysis is indicated.

Spain Protocol [9].

0 Treatment and prevention

Start volume replacement with saline at a rate of 400 mL / h (200-1000ml / h depending on the case and severity), with monitoring of central venous pressure.

Have a target diuresis of approximately 3mL/kg/h (200mL / h)

Correct hypocalcemia only in symptomatic patients (tetany or convulsions) or if the patient presents severe hyperkalemia.

Check urinary pH. If it is below 6.5, alternate each liter of saline with a liter of dextrose 5%, plus 100mmol bicarbonate. Avoid solutions containing lactate and potassium.

Consider treatment with mannitol (Up to 200g per day and up to a cumulative 800g). Check plasma osmolality and its variation. Discontinue if diuresis is not established (or <20 mL / h).

Keep volume replacement until no more myoglobinuria (evidenced by the clear urine or absence of blood in urine test)

Consider dialysis if refractory hypercalcemia above 6.5 mmol / L, symptomatic (evidenced in ECG), rapid elevation of serum potassium, oliguria (<0.5 mL / kg / h per 12h), anuria, volume overload or refractory metabolic acidosis (pH <7.1). [17]

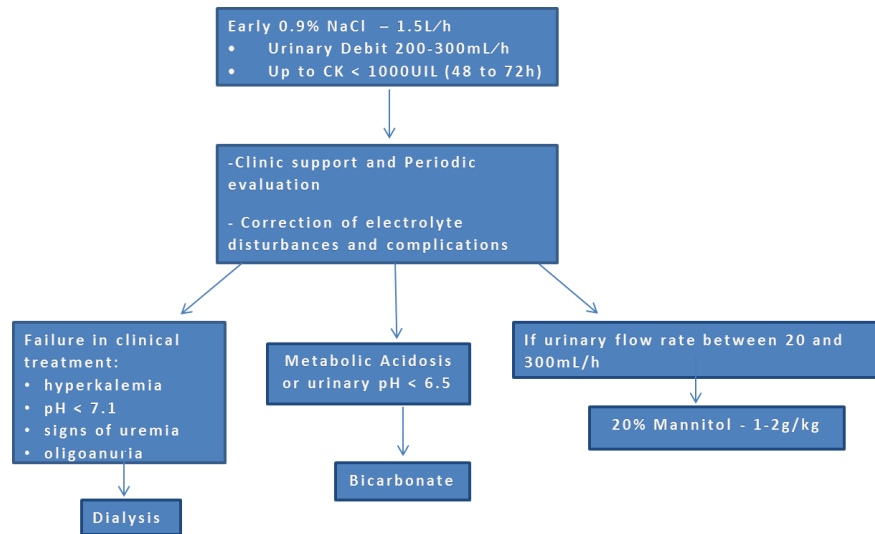
The Table 1 summarises the main points of the protocols evaluated.

Table 1: Details of the evaluated protocols (4,9,12,13).

	USP	SANTA CASA	USA	SPAIN
Diagnosis	Clinical and Lab	Clinical and Lab	Clinical and Lab	Clinical and Lab
Hydration	0,5-1L bolus	1,0-1,5L bolus (10-12L/24h)	1,5L/h	200-1000 mL/h
Alkalinization	1mEq/kg bolus 140mEq BIC into 1L dextrose 5%	100ml of BIC 8,4% + 100ml manitol 25% + 800 ml dextrose solution 5% at 1L/4h.	130mEq/L + 200ml/h	- 100mmol BIC + 1L dextrose 5%
Manitol	10% mannitol 15 to 45ml/h 5g / h.	100ml of BIC 8,4% + 100ml manitol 25% + 800 ml dextrose solution 5% at 1L/4h.	1 to 2g/kg - 5g/h	200g/24h - Max 800g
Dalisy	K > 6.5 mmol/L rapid elevation of serum K oliguria anuria volume overload pH <7.1	K > 6.5 mmol/L rapid elevation of serum K oliguria anuria volume overload pH <7.1	Volume overload K > 6.5 mEq/L pH < 7.1 signs of uremia	K > 6.5 mmol/L rapid elevation of serum K oliguria anuria volume overload pH <7.1
Complications	Hypocalcemia Hypercalcemia Volume overload	Hypocalcemia Hypercalcemia Volume overload	Hypocalcemia Hypercalcemia Volume overload	Hypocalcemia Hypercalcemia Volume overload

Below we suggest an protocol for early identification and treatment of rhabdomyolysis (chart 1).

Chart 1: Suggested Protocol.



IV. DISCUSSION

The main objective is to prevent acute renal injury and secondarily correct electrolytes disturbances and treat the cause of rhabdomyolysis [12].

The patient with this disease must be hospitalized in an emergency bad or ICU with monitoring and a well established venous access [14,15].

Preserving renal function is crucial in the acute phase of treatment, as well as reestablishing the metabolic functions of the body. In the 2013 review of Prof. Elizabeth J Scharman *et al*, is recommended an early volume replacement (within 6 hours). Hydration should be performed with 0.9% NaCl solution infused at a rate of 1.5 L / h, targeting a diuresis between 200 and 300 ml/h [16].

Such values of diuresis must be achieved in about at least 24 hours for a better prognosis. According to American literature, this hydration should be maintained until the values of CPK fell to below 1000 IU / L and according to Hospital Santa Casa de São Paulo and Hospital das Clínicas of USP university guidelines, it is recommended 48 to 72 hours hydration depending on clinical improvement and continuous decreases in CPK. If the CPK levels are not falling and the patient did not show any clinical improvement within 72 hours we considered in our protocol to maintain hydration until CPK levels are below 1000 IU / L [13,14, 15, 17].

The patient should be reassessed periodically in controlling complications of rhabdomyolysis and fluid replacement. Treatment should be individualised according to comorbidities, age and needs of each patient [4,9,10,16-18]. One way to optimize renal blood flow, mobilize interstitial fluid and reduce muscle edema is the use of mannitol. Mannitol is a diuretic with proximal tubes action and it's therapeutic use is controversial in rhabdomyolysis. There are no randomized studies with control groups made in humans, demonstrating their benefit [13,16,17].

However, nephroprotector mechanisms are described in the literature, such as decreased formation of tubular cylinder by the

excretion of heme protein; renal vasodilatation properties; reduction of oxidative stress because it is a free radical scavenger and acts as an osmotic agent in the transfer of fluid into the intravascular compartment, interstitial edema, and decreasing the risk of compartment syndrome. [4,22]

But at Brown et al's work, 2004, no statistically significant difference in preventing mortality, renal failure or the need for dialysis was found. This study analyzed 2083 patients over 5 years, victims of trauma, who had rhabdomyolysis, comparing treatment with hydration against treatment with hydration plus alkalization of urine and mannitol [4, 9,20].

The use of mannitol is considered beneficial in cases where the urinary flow is under 300 ml / h, by increasing or maintaining this flow rate. This medication should be administered into a 20% solution for about 1 to 2 g per kg. Mannitol may be used only in patients who have adequate urine output, in other words, above 20 mL / h. During the infusion of mannitol it is important to be aware of it's use complications as hypernatremia, thrombophlebitis, pulmonary edema and cardiac overload (especially in overdose). There is no consensus on the timing of discontinuation of the administration of mannitol, however this can be done through the establishment of greater than 300 mL/h associated with decreased muscle edema (if any) and clinical improvement in the patient's urine output overall [4,13,16].

In Scharman et al and Brown et al, the benefits of urine alkalization are unproven, but also did not become apparent harm and is considered positive by many experts (level of evidence D). The use of bicarbonate is based on alkalization of urine, thereby reducing the renal capillary vasoconstriction, improving renal filtration and by consequence the clearance, reducing kidney injury by decreasing the precipitation of myoglobin in the tubules therefore reducing the risk of hyperkalemia. The administration of sodium bicarbonate is intended to maintain a urine pH above 6.5 [16,19,21].

Alkalization may exacerbate early symptoms of rhabdomyolysis hypocalcemia. Administration can be accomplished in several ways. The book Emergências Clínicas of Santa Casa de São Paulo recommends a solution containing 100 mL of 8.4% sodium bicarbonate, 100 ml mannitol 25% and 800mL of glucose solution 5% infused 1 liter into 4 hours. One

bolus of 100 mL of 8.4% sodium bicarbonate can be utilized if the urine pH is below 6.5 (4,13).

However, we will follow international pipelines, in which it is recommended 140mEq infusion of sodium bicarbonate in 1 liter of glucose solution and an attack bolus of 100mEq of bicarbonate 8.4%. This process will continue until maintaining the urinary pH range above 6.5. Keeping alert for signs of hypocalcemia as convulsions and tetany. Measure serum potassium every 3-4 hours because there is a risk of hyperkalemia during bicarbonate infusion. The suspension should be made if in 4-6 hours of treatment initiation the urinary pH increase is not evidenced. [4,13,16,19,22]

In the failure of clinical treatment, the patient may progress to severe renal failure. This means maintenance of hyperkalemia (K greater than 6.5) metabolic acidosis (pH less than 7.1 blood), signs of uremia, oliguria or anuria; the patient should undergo hemodialysis or hemofiltration [13,23,24].

After this review of medical literature, it was observed that there is a consensus about the use of early hydration as the main form of preservation of renal function during the management of rhabdomyolysis.

Despite existing conflicts in the literature, most revisions suggest the use of mannitol and sodium bicarbonate only if there is an adequate indication and should be considered as supportive therapy.

Randomized controlled trials would be interesting, since definitions of diagnostic and therapeutic purposes.

V. CONCLUSION

After analyzing all the articles and reviews, it was observed that there is widespread use of early hydration as the primary form of preservation of renal function on the management of rhabdomyolysis. Although there are conflicts in the literature, most revisions suggests the use of mannitol and sodium bicarbonate only if an appropriate indication exists. So to conclude a definitive protocol and resolution of conflicts between different protocols, more randomized controlled studies are necessary.

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