Rhabdomyolysis

1. rhabdomyolysis (RM) is a syndrome caused by injury to skeletal muscle → leakage of intracellular contents (potassium, phosphate, CPK, urate, and myoglobin) into plasma that may be toxic to kidneys

2. clinical triad: muscle weakness, myalgias, and dark urine

3. myoglobin (Mgb) is an oxygen binding protein in muscle that accepts oxygen from circulating hemoglobin. After muscle injury, plasma Mgb levels may exceed the capacity of the normal clearing mechanisms (which includes haptoglobin binding) and Mgb can precipitate in glomerular filtrate causing renal tubular obstruction, direct nephrotoxicity, intrarenal vasoconstriction, and acute kidney injury. Mgb appears quickly in the blood and is rapidly cleared within 24 hours. If Mgb spills into the urine (myoglobinuria) it can cause urine to test positive for “blood.” Reference range: 0–85 ng/mL

4. creatine phosphokinase (CPK) AKA creatine kinase (CK) replenishes muscle ATP by catalyzing a reaction between creatine phosphate (in muscle) and ADP. The appearance of CPK in the blood lags behind Mgb by a few hours, peaks in 24–36 hours, decreases at 30–40% per day, and remains elevated for several days. It is used as a marker for the diagnosis and assessment of the severity of muscular injury. Reference range: 60–174 IU/L.

5. acute kidney injury (AKI) is due to:

a) decreased extracellular volume + vasoactive substances → renal vasoconstriction and

b) ferrihemate, which is formed from myoglobin at a pH< 5.6

6. vasoconstriction/ischemia deplete tubular ATP formation, enhancing tubular cell damage and myoglobin precipitation causes formation of obstructive casts

7. risk of renal injury is low when initial CPK levels are < 15,000–20,000 U/L (though may occur at lower levels in patients with sepsis, dehydration, or acidosis).

Etiology and epidemiology

1. trauma & muscle compression/crush → direct injury to sarcolemma & occlusion of muscular vessels

2. excluding trauma, neurosurgeons are most likely to encounter RM in the setting of prolonged operations, especially spine surgery in the prone position, but also possibly even with minimally invasive lateral approach [1)]

3. other nontraumatic etiologies: infection, metabolic derangement, neuroleptic malignant syndrome, malignant hyperthermia, drugs, EtOH, environmental toxins, extreme muscular activity, sickle cell trait

4. incidence of myoglobin-induced AKI in adult rhabdomyolysis (all causes) ranges from 17–35%

5. ≈ 28–37% of adult patient require short-term hemodialysis

6. rhabdomyolysis accounts for 5–20% of all adult cases of AKI

Management and treatment

Proactive intervention: for patients at risk for rhabdomyolysis (e.g. spine surgery lasting > 5 hours), it may be helpful to proactively check CPK & myoglobin (Mgb) levels post-op, and, when elevated, to aggressively hydrate before the full blown syndrome develops

Predictors of potential AKI include [2]:

1. peak CPK level > 6000 IU/L, and especially if > 15,000 IU/L

2. dehydration: hematocrit > 50, serum sodium level > 150 mEq/L, orthostasis, pulmonary wedge pressure < 5mm Hg, urinary fractional excretion of sodium < 1%

3. sepsis

4. hyperkalemia or hyperphosphatemia on admission

5. hypoalbuminemia

Treatment

There is no Level 1 evidence for the treatment of RM [3].

Traditionally, RM has been treated with IV fluids with bicarbonate (in an effort to alkalinize the urine) along with PRN diuretics. These adjuncts to IV hydration have been called into question, [4] and it appears that prompt recognition and appropriate volume replacement may be all that is neede to avoid AKI in most patients.

The following is one possible protocol for adults (modified [5] available online). In an adult with RM and CPK ≥ 5000 IU/L AND acute renal failure (Cr ≥ 2.9 mg/dl):

1. general measures:

a) ABCs, I/O monitoring (foley catheter), correction of electrolyte abnormalities, correction of underlying cause if possible to prevent end organ complications, invasive hemodynamic monitoring may be needed to ensure adequate volume resuscitation

b) minimize other potential renal stressors: nephrotoxic antibiotics, iodinated IV contrast, ACE inhibitors, NSAIDs… (Level III [6])

c) EKG if hyperkalemia present

2. the mainstay of treatment is expansion of extracellular volume →increase glomerular filtration rate (GFR), oxygen delivery and dilutes myoglobin and other renal tubular toxins

3. start with IV fluid (IVF): lactated ringers (LR) is preferred over NS (Level II [7]) to maintain urine output (UO) ≥ 1 ml/kg/hr

4. if this not possible with IVF alone, add sodium bicarbonate (NaHCO3) and mannitol as follows until CPK shows a steady downtrend or falls below 5000 IU/L or UO averages > 100 ml/hr for 12

consecutive hours

a) if serum sodium ≤ 147 mEq/L: use 1/2 NS + 100 mEq NaHCO3/L @ 125 ml/hr

b) if serum sodium > 147 mEq/L: use D5W+ 100 mEq NaHCO3/L @ 125 ml/hr

c) mannitol: 12.5 g IV q 6 hours

5. in patients receiving NaHCO3, check daily ABG & electrolytes

a) if serum pH< 7.15 or serum NaHCO3 ≤ 15 mg/dL: bolus with 100 mEq NaHCO3 and recheck ABG in 3 hours, repeat until pH is > 7.5 AND serum NaHCO3 is > 15

b) discontinue bicarbonate if pH≥ 7.5

c) hold NaHCO3 for hypernatremia

One of the late Malignant hyperthermia clinical features.

A maladaptive shift from fat to carbohydrate (CHO) oxidation during exercise is thought to underlie myopathy and exercise-induced rhabdomyolysis in patients with fatty acid oxidation (FAO) disorders. We hypothesized that ingestion of a ketone ester (KE) drink prior to exercise could serve as an alternative oxidative substrate supply to boost muscular ATP homeostasis. To establish a rational basis for therapeutic use of KE supplementation in FAO, we tested this hypothesis in patients deficient in Very Long-Chain acyl-CoA Dehydrogenase (VLCAD).

Five patients (range 17-45 y; 4M/1F) patients were included in an investigator-initiated, randomized, blinded, placebo-controlled, 2-way cross-over study. Patients drank either a KE+CHO mix or an isocaloric CHO equivalent and performed 35 min upright cycling followed by 10 minutes supine cycling inside a Magnetic Resonance scanner at individual maximal FAO work rate (fatmax; ~40% VO2 max). The protocol was repeated after a one-week interval with the alternate drink. Primary outcome measures were quadriceps phosphocreatine (PCr), Pi and pH dynamics during exercise and recovery assayed by in vivo 31 P-MR spectroscopy. Secondary outcomes included plasma and muscle metabolites and respiratory gas exchange recordings.

Ingestion of KE rapidly induced mild ketosis and increased muscle BHB content. During exercise at FATMAX, VLCADD-specific plasma acylcarnitine levels, quadriceps glycolytic intermediate levels and in vivo Pi/PCr ratio were all lower in KE+CHO than CHO.

These results provide a rational basis for future clinical trials of synthetic ketone ester supplementation therapy in patients with FAO disorders [8].

1)
Dakwar E, Rifkin SI, Volcan IJ, et al. Rhabdomyolysis and acute renal failure following minimally invasive spine surgery: report of 5 cases. J Neurosurg Spine. 2011; 14:785–788
2)
Ward MM. Factors predictive of acute renal failure in rhabdomyolysis. Arch Intern Med. 1988; 148: 1553–1557
3) 5) 6) 7)

Bada Alvaro, Smith Nathan. Rhabdomyolysis: Prevention and Treatment. 2018. http://www.surgicalcriticalcare. net/Guidelines/Rhabdomyolysis% 202018.pdf
4)

Brown CV, Rhee P, Chan L, et al. Preventing renal failure in patients with rhabdomyolysis: do bicarbonate and mannitol make a difference? J Trauma. 2004; 56:1191–1196
8)

Bleeker JC, Visser G, Clarke K, Ferdinandusse S, de Haan FH, Houtkooper RH, IJlst L, Kok IL, Langeveld M, van der Pol WL, de Sain-van der Velden MGM, Sibeijn-Kuiper A, Takken T, Wanders RJA, van Weeghel M, Wijburg FA, van der Woude LH, Wüst RCI, Cox PJ, Jeneson JAL. Nutritional ketosis improves exercise metabolism in patients with very long-chain acyl-CoA dehydrogenase deficiency. J Inherit Metab Dis. 2020 Jan 18. doi: 10.1002/jimd.12217. [Epub ahead of print] PubMed PMID: 31955429.