



Alkali therapy for prevention of acute kidney injury in rhabdomyolysis

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Rhabdomyolysis is a syndrome characterized by breakdown of skeletal muscle and leakage of cellular constituents, including electrolytes, myoglobin, and other cytoplasmic proteins, into circulation [1]. In the United States, the National Hospital Discharge Survey has reported 26,000 cases of rhabdomyolysis annually [2]. The etiology of rhabdomyolysis is diverse and includes trauma, therapeutic agents, substance abuse, infection, hyperthermia, toxins, genetic defects, and metabolic diseases [3]. Acute kidney injury (AKI) reportedly occurs in 14% to 46% of patients with rhabdomyolysis, and about 28% to 37% of adults with AKI require temporary hemodialysis [4]. Therefore, AKI is a serious complication of rhabdomyolysis, regardless of the cause. Early recognition and prevention of AKI are the most important steps in treatment of rhabdomyolysis. Myoglobin is known to be the main cause of AKI in rhabdomyolysis cases. The myoglobin leaked from damaged skeletal muscle accumulates in serum and is observed in urine as a reddish-brown substance when the serum myoglobin concentration exceeds 100 mg/dL [1]. Acidic urine and increased uric acid in the urine can precipitate inter-

action between myoglobin and Tamm-Horsfall protein, which results in the formation of casts in the tubules and impaired urine flow [1]. Myoglobin is a heme protein that contains iron as ferrous oxide. However, naked ferrous oxide in heme protein outside of the cell is easily oxidized to ferric oxide, because of a lack of effective intracellular antioxidant systems. In the oxidation process of ferrous oxide to ferric oxide, a hydroxyl radical is generated. This process of heme oxidation of myoglobin is known to be enhanced in a low pH environment [5]. Therefore, myoglobin deposited in acidic urine in the tubules releases reactive oxygen species and free radicals, leading directly to tubular injury [1]. Renal vasoconstriction is a further feature of rhabdomyolysis-induced AKI and is mediated by activation of various physiological pathways. The fluid trapped in the damaged skeletal muscle leads to a reduced intravascular volume, which promotes activation of the renin-angiotensin system, the sympathetic nervous system, and release of other vascular mediators, including vasopressin, endothelin-1, tumor necrosis factor- α , and thromboxane A₂, as well as myoglobin itself as a scavenging factor of nitric oxide [5]. F₂-isoprostanes, which are good *in vivo* markers of lipid peroxidation, are markedly increased in patients with rhabdomyolysis and are potent vasoconstrictors formed by

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the action of free radicals on arachidonic acid. Collectively, the acidic urinary environment increases tubular obstruction via formation of myoglobin-containing casts and oxidative stress-induced tubular injury/vasoconstriction via accelerated oxidation of ferrous myoglobin. Therefore, administration of sodium bicarbonate as alkali therapy has been recommended for reduction of myoglobin precipitation, redox cycling, and lipid peroxidation to prevent oxidative tubular injury and renal vasoconstriction [3]. However, there is little clinical evidence that urinary alkalization therapy using bicarbonate is better than administration of saline to prevent AKI [6]. In this issue of *Kidney Research and Clinical Practice*, Kim et al. [7] report a large retrospective propensity score-matched cohort study in which they examined whether bicarbonate therapy is better than non-bicarbonate therapy in 4,077 patients with rhabdomyolysis. They found that patients who received bicarbonate had a higher incidence of AKI, were more likely to need dialysis, and had a higher mortality rate and a longer hospital stay than those who did not. Furthermore, patients who received high-volume fluid therapy had worse renal outcomes and a lower survival rate than those who received low-volume fluid therapy. Despite not being a randomized controlled trial, this research is important, because its findings argue against the conventional view of therapies for rhabdomyolysis and are robust enough to warrant their dissemination to a wide audience, including practitioners in emergency medicine, internal medicine, and nephrology.

Contrast-induced AKI (CI-AKI) is similar to rhabdomyolysis-induced AKI in that iodinated contrast agents also induce tubular oxidative injury and renal vasoconstriction via inhibition of nitric oxide activity and production of F₂-isoprostanes in the same way as myoglobin in rhabdomyolysis-induced AKI. Alkali therapy for CI-AKI by administration of bicarbonate has been used in the clinical setting for a long time. Until now, there has been controversy regarding the therapeutic advantage of bicarbonate over saline. However, it is interesting to review how sodium bicarbonate infusion therapy has been evaluated in the past. CI-AKI is more common than rhabdomyolysis-induced AKI. Several small randomized controlled trials have demonstrated therapeutic superiority of bicarbonate over saline. A meta-analysis of these trials also revealed a lower incidence of CI-AKI with sodium bicarbonate-based hydration than with normal saline-based hydration [8]. However,

a retrospective cohort study that included 7,977 patients found that the incidence of CI-AKI was higher in those who received sodium bicarbonate than in those who did not, and remained higher after propensity score matching [9]. Finally, in 2018, the PRESERVE (Prevention of Serious Adverse Events Following Angiography) trial in high-risk patients found that intravenous administration of sodium bicarbonate was not superior to normal saline for the prevention of CI-AKI [10]. The largest and most sophisticated clinical trial in CI-AKI, PRESERVE had a randomized, double-blind, placebo-controlled design, and included more than 5,000 patients with and without diabetes, and estimated glomerular filtration rates in the range of 45.0–59.9 mL/min/1.73 m² and 15.0–44.9 mL/min/1.73 m², respectively. PRESERVE also excluded patients with an unstable baseline serum creatinine level, which made the study more feasible.

The PRESERVE study provides evidence that a saline hydration strategy is sufficient to prevent CI-AKI. In the future, we will need a large-scale, well-designed clinical trial in patients with rhabdomyolysis to determine the most suitable hydration strategy for prevention of rhabdomyolysis-induced AKI.

Conflicts of interest

The authors have no conflicts of interest to declare.

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