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Renal tubular dysfunction in Bothrops venom-induced acute kidney injury

Polianna Lemos Moura Moreira Albuquerque[1], Geraldo Bezerra da Silva Junior[2], Gdayllon Cavalcante Meneses[3], Alice Maria Costa Martins[4], Jacques Raubenheimer[5], Fathima Shihana5, Nicholas Buckley[5] and Elizabeth De Francesco Daher[1]

[1]Medical Sciences of Post-Graduate Program, Department of Internal Medicine, Federal University of Ceara. Fortaleza, Ceara, Brazil. [2]Collective Health Post-Graduate Program, School of Medicine, University of Fortaleza. Fortaleza, Ceara, Brazil. [3]Pharmacology Post-Graduate Program, Department of Physiology and Pharmacology, Federal University of Ceara. Fortaleza, Ceara, Brazil. [4]Department of Physiology and Pharmacology, Federal University of Ceara. Fortaleza, Ceara, Brazil. [5]Clinical Pharmacology, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia.

Objective: *Bothrops sp* are the most common snakes associated with acute kidney injury (AKI) in Latin America. The aim of this study is to investigate renal tubular function and novel biomarkers in *Bothrops*-induced AKI.

Methods: This is a pilot study of patients with *Bothrops*-induced AKI admitted to a reference hospital in Brazil from December 2015 to December 2016. AKI was defined according to the KDIGO criteria. Novel biomarkers were compared to results obtained from 13 healthy volunteers. AKI and non-AKI patients were also compared. ELISA (R&D systems Inc., USA) was used to measure biomarkers from blood ($_{s}$NGAL) and urine ($_{u}$NGAL, $_{u}$MCP-1, $_{u}$KIM-1, $_{u}$VCAM-1 and $_{u}$IL-6). Urinary concentration defects were diagnosed if the urine osmolality (U_{osm})/plasma osmolality (P_{osm}) ratio was <2.8. Other renal tubular functions measured were fractional excretions of sodium (FE_{Na}), urea (FE_{Urea}), potassium (FE_{K}), urinary concentration of sodium ($_{Ur}$[Na]) and transtubular potassium concentration gradient (TTKG).

Results: 63 patients were included, and 22 (35%) developed AKI. Epidemiological characteristics were similar in both groups. AKI patients had lower serum sodium (138.6 ± 1.2 vs 142 ± 0.6mEq/L; p=0.01), haemoglobin (11.06 ± 0.45 vs 12.40 ± 0.28g/dl; p=0.011), haematocrit (31.52 ± 1.38 vs 36.36 ± 0.86%; p=0.003) and Uosm/Posm (1.12 ± 0.18 vs 1.80 ± 0.15; p=0.006). AKI had higher FEK on admission (21.7 ± 3.8 vs 8.4 ± 4.5%; p=0.003). The activated partial thromboplastin time (APTT) on admission, was significantly longer in the AKI group (p=0.011). Incoagulable blood (diagnosed as APTT>180s) was an independent risk factor for AKI (OR 26.6, p=0.0491). However, FENa (2.29 ± 0.73 vs 1.26 ± 0.25%; p=0.2), FEUrea (44.6 ± 5.7 vs 42.3 ± 4.1%; p=0.75), Ur[Na] (97 ± 13 vs 113 ± 13 mEq/L; p=0.44) and TTKG (6.9 ± 1.0 vs 5.5 ± 0.73; p=0.27) were similar. In the AKI group, uMCP-1 (471 ± 60 vs. 289 ± 41pg/ml; p=0.014), and uNGAL (15.3 ± 1.3 vs. 10.3 ± 1.1ng/ml; p=0.006), were significantly higher. Urinary proteinuria and FENa correlated with uMCP-1 and uNGAL.

Conclusion: Bothrops-induced AKI causes tubular dysfunction manifesting as inability to concentrate urine even without significantly reduced glomerular filtration rate. Higher levels of uMCP-1 and uNGAL likely represent early tubular and glomerular damage. Abnormal fractional excretion of electrolytes and Ur[Na] >40mEq/L suggest acute tubular necrosis. Normal TTKG indicates reduced activation of the renin-angiotensin system and points to hypervolemic status in these patients.