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ORIGINAL RESEARCH ARTICLE

COMPARISON BETWEEN RHABDOMYOLYSIS INDUCED AND SEPTIC ACUTE KIDNEY INJURY IN CENTRAL NEPAL

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ABSTRACT

Background: Acute kidney injury (AKI) is one of the most serious complications of rhabdomyolysis (RM). We studied the clinical manifestations and prognosis of rhabdomyolysis induced AKI and compared it with septic AKI among hospitalized patients.

Methods: A prospective study was conducted at Chitwan Medical College between January 2017 to June 2018 to compare AKI secondary to rhabdomyolysis (RM-AKI) and sepsis (SA-AKI). AKI was diagnosed as per Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines. Rhabdomyolysis was diagnosed if serum creatinine phosphokinase raised >5 times the upper limit of normal level and sepsis as an increase of two or more points in the Sequential Organ failure Assessment (SOFA) score with the evidence of infection.

Results: A total of 145 patients with AKI (21 with RM and 124 with sepsis) were included in the study. Mean age of the patients was 43.7 years with majority (54%) being males. Wasp bite and bee sting combined together (47.6%) were the most common causes for RM-AKI whereas pneumonia accounted for 46.6% of the septic AKI. Serum creatinine (SCr) at admission and at discharge were 3.8 and 1.4 mg/dL respectively in RM-AKI group; and 2.4 and 1.6 mg/dL in septic AKI group. Duration of stays in the hospital (9.2 versus 6.4 days) and ICU (4.2 versus 3.7 days) were longer in RM than in septic AKI. In hospital mortality was 4.8% in RM and 8.9% in septic AKI.

Conclusions: This study has found that, despite a longer duration of hospital stay, RM-AKI had a lower in-hospital mortality than septic AKI.

INTRODUCTION

Rhabdomyolysis is a clinical syndrome characterized by muscle necrosis and the release of intracellular toxic muscle constituents into the interstitial space and the circulation.[1] The outcomes following rhabdomyolysis might vary from asymptomatic elevations of creatinine kinase (CK) to the derangement of multiple organ functions including hypovolemia, acidosis, acute kidney injury (AKI) and disseminated intravascular coagulation (DIC),[2] out of which AKI associated with myoglobinuria is the most serious complication with worse prognosis. Due to a wide variation in the definitions and clinical scenarios, it is difficult to establish the true incidence of AKI in rhabdomyolysis. AKI due to rhabdomyolysis occurs in 13 to 50% of all cases[3,4] where mortality rates might rise up to 59% in critically ill patients.[5] The causes of rhabdomyolysis may be classified as traumatic, non-traumatic exertional, and non-traumatic non-exertional causes.[6] The pathophysiology of rhabdomyolysis induced AKI is believed to be triggered by myoglobin[7] with three different pathophysiologic mechanisms- renal vasoconstric-

tion, formation of intra-tubular casts and the direct toxicity of myoglobin to renal tubular cells.[8-10] Serum levels of CK correlate with the severity of rhabdomyolysis but it might not be an ideal marker to predict risk of AKI.[11,12] The electrolyte abnormalities that can occur with rhabdomyolysis include hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia and high anion-gap metabolic acidosis.[13,14] In a retrospective observational study, the best cutoff values for prediction of AKI in rhabdomyolysis were CK >773 U/l, serum myoglobin >368 µg/l and urine myoglobin >38 µg/l, respectively.[15]

Sepsis is a life-threatening clinical syndrome characterized by organ dysfunction caused by a patient's dysregulated response to infection.[16] Sepsis has been documented as the most important cause of AKI in the intensive care unit (ICU) with an estimated association of sepsis with more than half of AKI. Acute renal tubular apoptosis was demonstrated in septic AKI.[17] It has been documented that the requirement of dialysis supports due to septic AKI can reach as high as 20%.[18]

Although there are few studies done in Nepal on septic AKI[19,20] and few case series and reports of rhabdomyolysis induced AKI,[21,22] there is a paucity of information on comparison between the clinical manifestations and outcomes of rhabdomyolysis induced acute kidney injury and septic AKI. So, this study was conducted with an aim to find out the etiologies, severity, biochemical changes, clinical course and prognosis of rhabdomyolysis induced AKI (RM-AKI) and compare it with sepsis associated AKI (SA-AKI) among hospitalized patients.

METHODS

This descriptive observational study was conducted in the Nephrology Unit at Chitwan Medical college between January 2017 and June 2018. All patients irrespective of the place of admission (general wards or critical care units) who met the criteria of AKI as per Kidney Disease Improving Global Outcomes (KDIGO) definition during the study period were included in the study. Ethical clearance was obtained from the Institutional Review Committee of Chitwan Medical College (CMC-IRC) before initiation of the study. Enrolled subjects were aware of the investigational nature of the study and informed written consent was taken before enrolling the participants. AKI was defined according to KDIGO 2012 guideline as a rise in serum creatinine by more than 0.3 mg/dL from baseline or decrease in urine output less than 0.5 ml per kilogram of body weight for 6 hours.[23] Rhabdomyolysis was diagnosed if serum creatinine phosphokinase raised more than 5 times the upper limit of normal level[24] and sepsis as an increase of two or more points in the sequential organ failure assessment (SOFA) score with the evidence of infection.[25] Glomerular filtration rate (GFR) was estimated by using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.[26] Four variables like serum creatinine, age, sex and race are used to estimate GFR by MDRD equation. Complete recovery (CR) of AKI was defined as return of latest serum creatinine (SCr) to normal range (<1.2 mg/dL) or within 20% of baseline SCr and partial recovery (PR) as the SCr >1.5 mg/dL without the need of long-term dialysis.

Patients who met the above-mentioned definitions of AKI, rhabdomyolysis and sepsis and consented to participate in the study were included in the study. Patients who were younger than 18 years and already diagnosed to have chronic kidney disease (CKD) were excluded from the study.

Preformed pro-forma was used to record the details that included detailed history of diabetes, hypertension, recent surgery, any conditions causing body fluid loss, use of nephrotoxic medication. Physical examination was done thoroughly and the findings were recorded. Details of investigations findings, which included complete blood count (CBC), renal function test (RFT), blood sugar level, serum uric acid, calcium and phosphate level, arterial blood gas analysis, urine routine and microscopic examination, chest X-ray and when feasible screening ultrasound of the abdomen and pelvis were recorded. Kidney biopsy was done if clinically indicated. Urine output in patients admitted in the ICU was done on hourly basis and in patients admitted in general wards in daily basis. AKI staging was done according to KDIGO guideline.[23] Details about the requirement of inotropic support including dose and duration was recorded. Decision about the initiation of hemodialysis was made by the nephrologist as per the clinical indications. Requirements, indications and total sessions of hemodialysis including the type of vascular access was recorded. The patients were monitored daily till they were discharged from the hospital and the outcome of the patients was recorded.

The data was entered in excel format, which were later analyzed by using statistical analysis system (SAS) University Studio package. Results of the study were expressed in frequency and percentage. One-way analysis of variance (ANOVA) was used to compare rhabdomyolysis induced and septic AKI. Student t-test was used to compare mean values between the study groups. Data are expressed as odds ratio (ORs) and 95% confidence intervals (CIs). Data with p-value <0.05 were considered significant.

RESULTS

A total of 145 patients with AKI (21 with RM-AKI and 124 with SA-AKI) were included in the study. Mean age of the patients was 43.7 years and majority (54.5%) aged between 30 to 49 years. Fifty-four percentage of patients were males. Wasp bite and bee sting combined (47.6%) were the most common causes for RM-AKI (Figure 1), whereas pneumonia accounted for 46.6% of the SA-AKI.

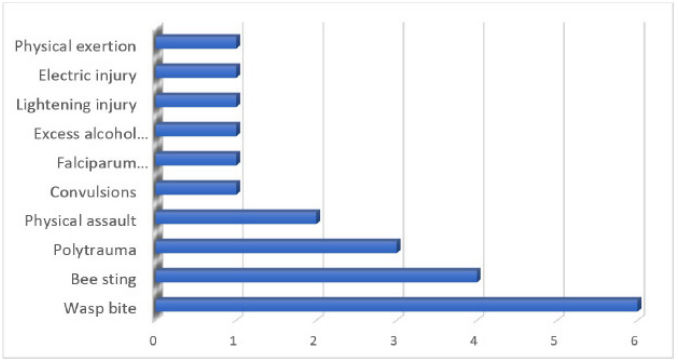

Figure 1: Etiologies of rhabdomyolysis

Among the patients with RM-AKI, most common clinical symptoms were muscle pain (95.23%), body weakness (85.71%), nausea/vomiting (76.19%), oliguria (47.61%), dark urine (38.09%), and fever (19.04%). Mean level of CK in this group of patients was 31644±35056 (range: 1100 to 123000) mcg/L at presentation and 148.5±80 (range: 100 to 351) mcg/L at discharge.

Table 1: Comparison between rhabdomyolysis induced and septic AKI

Variables		Rhabdomyolysis induced AKI (n=21)		Septic AKI (n=124)		p-value
		Count (%)	95% CI	Count (%)	95% CI	
Male gender		19 (90.48%)	76.78-100.00	59 (47.585%)	38.67-56.49	0.0003
Age group	18-29 Yrs	1 (4.76%)	0.00-14.70	23 (18.55%)	11.61-25.49	0.0008
	30-49 Yrs	20 (95.24%)	85.3-100.00	59 (47.58%)	38.67-56.49	
	50-69 Yrs	0	0.00-0.00	31 (25.00%)	17.27-32.73	
	70-85 Yrs	0	0.00-0.00	11 (8.87%)	3.80-13.95	
AKI stage	Stage I	1 (4.76%)	0.00-14.70	13 (10.48%)	5.02-15.95	0.2419
	Stage II	9 (42.86%)	19.77-65.94	69 (55.65%)	46.78-64.51	
	Stage III	11 (52.38%)	29.09-75.68	42 (33.87%)	25.42-42.32	
Oliguria		13 (61.90%)	39.25-84.56	83 (66.94%)	58.54-75.33	0.6522
Hemodialysis		6 (28.57%)	7.50-49.64	27 (21.77%)	14.41-29.14	0.7387
Inotropic support		1 (4.76%)	0.00-14.70	50 (40.32%)	31.57-29.08	0.0010
Outcome	Complete recovery	10 (47.62%)	24.32-70.91	64 (51.61%)	42.69-60.53	0.7004
	Partial recovery	10 (47.62%)	24.32-70.91	49 (39.52%)	30.79-48.24	
	Mortality	1 (4.76%)	0.00-14.70	11 (8.87%)	3.80-13.95	

Serum creatinine (SCr) at admission and at discharge were 3.8 and 1.4 mg/dL respectively in RM-AKI group; and 2.4 and 1.6 mg/dL in SA-AKI group (Figure 2). Estimated glomerular filtration rate (eGFR) at admission and at discharge were 24.80±13.34 (95% CI 18.72 to 30.87) and 61.21±18.71 (95% CI 52.70 to 69.73) respectively in the RM-AKI group; and 36.14±21.82 (95% CI 32.26 to 40.02) and 55.74±23.13 (95% CI 51.62 to 59.85) respectively in the SA-AKI group.

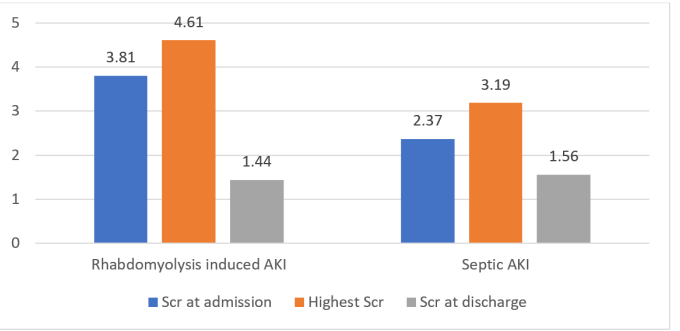

Figure 2: Comparison of serum creatinine in two groups

Stage 3 AKI was seen 52.38% of patients in RM-AKI and 33.87% of patients in SA-AKI group with indication of hemodialysis for 28.6% and 21.8% of patients in two groups respectively. Duration of stays in the hospital (9.2 versus 6.4 days, p=0.0026) and ICU (4.2 versus 3.7 days, p=0.4946) were longer in RM-AKI than in SA-AKI. In hospital mortality was 4.8% in RM and 8.9% in septic AKI. Achievement of complete recovery, defined as the latest SCr returned to normal range (<1.2 mg/dL) or within 20% of baseline SCR, was better in septic AKI (51.6% versus 47.6%). Mean days of hospital stay was 9.24 and ICU stay was 4.19. Only one patient died during the hospital stay. Comparative analysis of different parameters is shown in Table 1.

DISCUSSION

This study compared the etiologies, clinical parameters and outcome among patients with acute kidney injury secondary to rhabdomyolysis (RM-AKI) and sepsis (SA-AKI). There is paucity of studies done on rhabdomyolysis induced AKI and only a few observational and retrospective studies have been published to explore the occurrence of rhabdomyolysis in critically ill patients.[5,27,28]

Acute kidney injury is one of the most serious complications of rhabdomyolysis. Almost 10 to 50% of patients with severe rhabdomyolysis develop AKI[3, 29, 30] with reported mortality rates ranging between 13-59%.[29,31] The main mechanism of kidney damage in patients with rhabdomyolysis is the massive release of myoglobin into the circulation, with myoglobinuria.[32] A number of etiologies have been attributed as the causes of rhabdomyolysis such as trauma, extreme physical exercise, hypophosphatemia, drugs, infections, hypokalemia, and others.[30] In our study, two most common causes of rhabdomyolysis were wasp bite (28.57%) and bee sting (19.04%). Chitwan district that lies in the central part of Nepal where this study has been conducted is well known for bee keeping. Additionally, many people come in contact accidentally with the wild bees harvesting nearby their houses. Moreover, people residing in the rural areas also have the habit of hunting wasps in the jungle to eat their larva, which is consumed as a chief source of protein. Such habits have kept the people more vulnerable to sustain wasp bite and related complications such as hemolysis, rhabdomyolysis, coagulation, cardiac, pulmonary, hepatic, and nervous system disorders, hypertension, and AKI.[33-36] Sigdel et al reported a case series of 18 patients from a tertiary hospital in Kathmandu, Nepal who sustained acute renal failure (ARF) requiring dialysis following wasp bite.[37] The number of admitted patients who sustained rhabdomyolysis without AKI could have been much higher than what we have reported in this study because we have included only those patients who developed AKI.

Sepsis, which is a clinical condition characterized by organ dysfunction secondary to patient's dysregulated response to infection, is associated with AKI in up to 60-70% of patients,[38-40] and it is well understood that the patients with sepsis complicated by AKI have higher mortality than those without AKI.[41] Although the pathophysiology is poorly understood, the contributing factor for SA-AKI could be the renal hypotension associated with ischemia, inflammation and apoptosis.[42,43] Although, there is no specific etiology of sepsis that has higher preponderance to develop SA-AKI, in our study pneumonia was the most common etiology (46.6%) followed by urosepsis, other infections like scrub typhus, leptospirosis, and wound infection.

Majority of the patients in this study were males (54%). The predominantly higher proportion of males in the RM-AKI group (90.48%) could be attributable to the fact that males are exposed more to the outdoor activities than the females, which could have made them vulnerable to develop rhabdomyolysis. Male predominance in the incidence and prevalence of rhabdomyolysis has been reported to range between 70-84% in different studies.[44,45] Mean age of the patients was 43.7 years and majority (70.34%) of the patients were younger than 50 years.

We also analyzed the level of CK among patients with RM-AKI. The mean CK level was 31644 mcg/L at presentation and 148.5 mcg/L at discharge. The most specific laboratory marker of rhabdomyolysis was elevated plasma CK level, with values from 5 to 10 times the upper limit of normal frequently used to define rhabdomyolysis.[30] Following the onset of muscle injury, serum CK begins to rise within 2 to 12 hours and reaches its maximum within 24 to 72 hours. A decline in its level is usually seen in three to five days of cessation of muscle injury. CK has a serum half-life of about 1.5 days and the level decreases at a relatively constant rate of about 40 to 50 percent of the previous day's value.[46] In patients whose CK does not decline as expected, continued muscle injury or the development of a compartment syndrome may be present.

Acute kidney injury in this study was classified into 3 stages according to the KDIGO guideline. Among the patients with RM-AKI, stage 3 AKI was most frequently seen (52.38%) followed by stage 2 (42.86%) and stage 1 (4.76%). Whereas in SA-AKI group stage 2 was the most common (55.65%) followed by stage 3 (33.87%) and stage 1 (10.48%). Although, the estimated GFR was better in SA-AKI than the RM-AKI group (36.14 versus 24.80 ml/min) at the time of admission, there was better improvement of this parameter in RM-AKI group at the time of discharge (61.21 versus 55.74 ml/min). In patients with rhabdomyolysis, CK levels, hypoalbuminemia, decreased prothrombin time, and metabolic acidosis on admission have been described as independent risk factors for AKI.[47] Among many factors, initial serum creatinine level has been demonstrated as an independent predictor of outcome in patients with rhabdomyolysis.[33] Sepsis has been described as an independent factor to predict AKI in patients admitted in the ICU.[48] Renal replacement therapy (RRT) in the form of hemodialysis was indicated for 28.7% of patients in RM-AKI and 21.77% in SA-AKI group. The requirement of inotropic support was significantly higher in the SA-AKI than in the RM-AKI group (40.32% versus 4.76%, p=0.0010).

We have found better renal recovery among patients with RM-AKI than in the SA-AKI (95.24% versus 91.13%) with a higher mortality rates in the SA-AKI group. Among patients with rhabdomyolysis age, female sex, cause of rhabdomyolysis, and values of initial creatinine, creatine phosphokinase, phosphate, calcium, and bicarbonate have been documented as the independent predictors of the composite outcome.[49] Baseline SCr level and progressive KDIGO stage of AKI are described as the independent risk factors for worse renal outcome in SA-AKI.[50]

Although this was a first comparative study between RM-AKI and SA-AKI among Nepalese patients, it has some limitations. First of all, this was a single centered study that included only the adult population and its findings might not be generalized among the pediatric population. We also lacked behind to provide and develop predictive models for the renal and overall outcome in two groups. Despite these limitations, we still believe this study would provide a strong baseline framework to design further large and multicentric studies to establish the national level information in these clinical parameters.

CONCLUSION

This study done in central Nepal has tried to establish the comparative analysis between rhabdomyolysis induced and septic AKI. We have found that, despite a longer duration of hospital stay, RM-AKI had a lower ICU stay and in-hospital mortality than septic AKI.

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