

Study on Comparing Serum Cystatin-C and Serum Creatinine in Detecting Acute Kidney Injury in Snake Bite Patients

¹R.Balajinathan, ²V.N.Alagavenkatesan, ³G.Gurunamasivayam, ⁴Narendra Prasad, ⁵M.Rathinam*

ABSTRACT

Snakes that cause kidney injury are myotoxic and hemotoxic snakes, it causes intravascular hemolysis, rhabdomyolysis, hemorrhage and disseminated intravascular coagulation. Considering the drawback of serum creatinine in predicting AKI (Acute Kidney Injury), newer biomarker should be used to detect AKI early so that timely intervention can be done. This study is to be conducted among 50 snake bite patients with acute kidney injury who are admitted at the Govt. Rajaji hospital, Madurai. Mean age (\pm S.D): 37.84 (15.84) years, minimum: 14 years, maximum: 70 years. Serum creatinine at 24 hours after snake bite in this study was 1.57 ± 0.8 mg/dl. Serum cystatin C value at 24 hours after snake bite in this study was 1.82 ± 0.5 mg/dl. 56% (n=26) of the study subjects were predicted as having early AKI according to e-GFR based on creatinine at 24 hours. 94% (n=47) of the study subjects were predicted as having early AKI according to e-GFR based on cystatin-C at 24 hours. About 20 participants (40%) who were not detected with early AKI by creatinine based e-GFR were detected as having early AKI by cystatin-C based e-GFR.

KEY WORDS : Renal failure, Snake bite, Creatinine, GFR

Introduction

AKI is a variable group of diseases with same features; it does not denote a single condition. It is associated with changes in electrolyte and acid base status of the blood. In developing countries condition like acute diarrheal diseases, Malaria and Leptospirosis accounts

for the majority of AKI cases [1-6]. It is seen in 30% of ICU patients and 5% of in patients. It is mostly asymptomatic and can be diagnosed by increase in BUN and creatinine. Urine output < 400 ml is oliguria which is seen in only 50% of patients. AKI increases the mortality and increases duration of hospital stay. AKI can be identified by serial measurement of blood urea nitrogen and creatinine. GFR can fall without increase in serum creatinine in patient with reduced muscle mass especially in elderly patient [7-11].

Snake bite poisoning is common in India. It occurs when people work in bare foot in fields or while walking at night. 1.2 to 5.5 million of snakebite occurs every year all

¹Professor, ^{2,3}Assistant professor, ^{4,5}Postgraduate student,
Department of General Medicine, Madurai Medical College, Madurai.

*Corresponding Author:

Dr.Rathinam.M,
Post graduate of General Medicine,
Madurai Medical College,
Madurai,Tamilnadu -625020.
E-mail id: drrathinam86@gmail.com
Telephone number: +919789910842

over the world. 20,000 to 94,000 deaths are reported. When envenomation occurs, it results in complications such as renal failure. Renal failure is in the form of acute tubular necrosis. Bilateral cortical necrosis is associated with poor prognosis. Out of the 3000 species of snakes only 15% are poisonous. Snakes are poikilotherms and live in a region with temperature around 25 to 35 degrees. Around 97% snake bites are seen in extremities. Snake bites are common in men. Out of poisonous snake bites 85% are hemotoxic [12-14].

Renal injury is one of the most common causes of death among patients who survived the early phase. Cause of AKI in Russell's viper bites is toxic nephropathy and blood pressure alteration. Chronic kidney disease is seen after bilateral cortical necrosis, panhypopituitarism and diabetes insipidus have been reported in Russell's viper bites. Kidneys are affected in different spectrum in snakebite. Clinical manifestations are proteinuria, hematuria, pigmenturia and acute kidney injury[15]. Hemotoxic and myotoxic snake bites are the causes of acute kidney injury. In India, Russell's viper and Echis carinatus bites are leading causing of AKI and the incidence of AKI is 13-32%.The mechanism of AKI are prolonged hypotension, disseminated intravascular coagulation, intravascular hemolysis, myoglobinuria and direct damage to the tubules [16].

Materials and Methods

This study were conducted among 50 snake bite patients with acute kidney injury who are admitted at the Govt. Rajaji hospital, Madurai. Patients with age more than 13 years are included in the study and those with history of chronic kidney diseases, diabetes, hypertension, chronic liver disease, patients received nephrotoxic drugs are excluded from study. Specimens are collected using standard vein-puncture techniques. The samples were

assayed immediately after collection or samples were stored at -20^o C Degree. The extracted sera are used for assessing serum cystatin C level using sandwich enzyme immunoassay ELISA technique.

Results

50 hemotoxic snake bite patients with acute kidney injury in the age group of >13 years, who are admitted in Govt.Rajaji Hospital Mean age (\pm S.D): 37.84 (15.84) years, minimum: 14 years, maximum: 70 years. About 60%(n=30) of the study subjects were in the age group of less than 40 years(Table-1). Majority of the study subjects were males (64%)(n=32) while the remaining 36%(n=18) were females(Table-2). 56%(n=28) of the study subjects were predicted as having early AKI according to e GFR based on creatinine at 24 hours (Table-3). Mean were Serum creatinine-1.57,SD-0.822,minimum-0.5,maximum-2.9.94%(n=47) of the study subjects were predicted as having early AKI according to e GFR based on cystatin-C at 24 hours (Table-4). Mean cystatin-c at 24 hours were-1.82,SD-0.513,minimum,0.7,maximum-3.0.About 20 participants (40%) who were not detected with early AKI by creatinine based e-GFR were detected as having early AKI by cystatin-C based e-GFR(Table-5). There was a statistically significant positive linear correlation indicating that the fall in serum creatinine levels are reflected in serum cystatin-C levels as well(Table-6).

Table.No. 1: Age distribution of the study population (n=50)

Age group	Frequency	Percent
<20 years	8	16
21-30 years	9	18
31-40 years	13	26
41-50 years	8	16
51-60 years	6	12
61-70 years	6	12
Total	50	100.0

Table.No. 2: Gender distribution of the study population (n=50)

Gender	Frequency	Percentage
Female	18	36
Male	32	64
Total	50	100

Table.No. 3: Early AKI as predicted from e GFR based on creatinine at 24 hours (n=50)

Based on creatinine e GFR at 24 hrs	Frequency	Percentage
Early AKI	28	56
No AKI	22	44
Total	50	100

Table.No. 4; Early AKI as predicted from e-GFR based on cystatin-C at 24 hours (n=50)

Based on cystatin-C e-GFR at 24 hrs	Frequency	Percentage
Early AKI	47	94
No AKI	3	6
Total	50	100

Table.No. 5 Early AKI according to e-GFR based on serum creatinine and cystatin-C at 24 hours (n=50)

Prediction of early AKI at 24 hours		cystatin-C e-GFR at 24 hrs n (%)		Total
		No AKI		
Creatinine based e-GFR at 24 hrs n (%)	AKI	27 (96.4)	1 (3.6)	28 (100)
	No AKI	20 (90.9)	2 (9.1)	22 (100)
Total		47 (94)	3 (6)	50 (100)

Kappa (measure of agreement): 0.061, p value: 0.415

Table.No. 6 Early AKI according to e-GFR based on serum creatinine and cystatin-C at 24 hours (n=50)

Correlation		Serum cystatin-C at 24 hr
Serum creatinine at 24 hr	Pearson Correlation	0.473
	p value	.001

Discussion

The study subjects were the patients who were admitted with complaints of snake bite in medical ward in Govt. Rajaji Hospital. The study subjects were not only from the Madurai City, they were from whole of the Madurai District comprising both the rural and the urban population, since Govt. Rajaji Hospital is tertiary care hospital and the referral centre. This study has enrolled a total of 203 snake bite patients who were admitted in medical ward during the period of July 2013 to December 2013(6 months) of which 50 patients developed AKI, and were selected for this study.

Age distribution in study subjects

In this study, out of the 50 patients, the mean age was 37.84 ± 15.84 years (Table.No.1). The minimum age was 14 years and the maximum was 70 years. About 60% of the study subjects were in age group of less than 40 years and 24% were in the age group above 60 years. Most of the patients in the age group of less than 40 years are affected by AKI. In a study done by Qiang li et al. [17] in china, the mean age of the study subjects was 38 years and the total number of study subjects was 71. In a study done by Kumaresan et al. in Thanjavur had enrolled 106 patients in the study with the mean age of 50 years [9]. In this study, most of the patients admitted with snake bite are in the age group of less than 40 years there is proportionate increase in AKI in this group.

Serum creatinine distribution

Serum creatinine at 24 hours after snake bite in this study was 1.57 ± 0.8 mg/dl. The minimum value of serum creatinine was 0.5 mg/dl and the maximum concentration of serum creatinine was 2.9mg/dl. In a study conducted by Herget-Rosenthal et al in New Delhi [16, 18], 44 patients were enrolled in this study and the mean concentration of serum creatinine was 1.57mg/dl. In a study done by Murty et al [19], in Mumbai, had 130 patients with mean concentration of serum creatinine was 2.08 mg/dl. In a study done by Kumaresan et al in Thanjavur had enrolled 106 patients in the study, the mean concentration of serum creatinine was 3.39mg/dl.

In this study serum creatinine value at 72 hours met the AKI criteria by AKIN criteria. Out of 50 patients in this study, 22 patients were in AKIN stage II (More than 2 to 3 fold increase in serum creatinine from baseline) and 28 patients were in AKIN stage III (More than 3 fold increase in serum creatinine from baseline (or) Serum creatinine more than or equal to 4 mg/dl (or) Sudden increase in Serum creatinine of 0.5 mg/dl (or) Patient who receives renal replacement therapy). The mean concentration of serum creatinine at 72 hours in this study was 4.39 ± 2.31 mg/dl. The minimum concentration was 1.45mg/dl and the maximum concentration was 8.12 mg/dl.

Serum cystatin c distribution

Serum cystatin C value at 24 hours after snake bite in this study was 1.82 ± 0.5 mg/dl . The minimum concentration of serum cystatin C was 0.7 mg/L and the maximum concentration of serum cystatin C was 3 mg/L. In a study conducted by Herget-Rosenthal et al in New Delhi, 44 patients were enrolled in the study, the mean concentration of serum cystatin C was 1.79mg/L [16]. In a study done by Kumaresan et al. [9] in Thanjavur

had enrolled 106 patients in the study, the mean concentration of serum cystatin C was 2.29 mg/L. In a study conducted by Mi Yeon Chung et al. [20] in Korea, 53 patients were included and the mean concentration of serum cystatin C was 1.3 mg/L.

Serum cystatin C value at 72 hours after snake bite in this study was 4.1 ± 1.14 mg/dl. The minimum concentration of serum cystatin C was 1.61 mg/L and the maximum concentration of serum cystatin C was 6.9 mg/L

Pearson correlation coefficient

In this study Pearson correlation coefficient(R) for Serum creatinine and serum cystatin C is 0.473 and the P value is 0.001. There was a statistically significant positive linear correlation indicating that the fall in serum creatinine levels are reflected in serum cystatin-C levels as well. In a similar study done by Murty et al [19]. In Mumbai which had 130 patients with AKI, Pearson correlation coefficient(R) for Serum creatinine and serum cystatin C is 0.735 and the P value is <0.01. In both these study Pearson correlation coefficient is positive and statistically significant, indicating that there is positive linear correlation between serum creatinine and serum cystatin C, fall in serum creatinine levels are reflected in serum cystatin-C levels as well.

Kappa (measure of agreement)

Kappa is a statistical measure to assess the reliability of agreement between a fixed numbers of raters when assigning categorical ratings to a number of items. Kappa value in this study is 0.061 and the P value is 0.415. Measure of agreement between these two criteria was not statistically significant and hence there is wide disparity in detection of early AKI by using creatinine and cystatin-C based e-GFR.

Conclusion

Out of 50 AKI patients in this study, 22 patients were in AKIN stage II and 28 patients were in AKIN stage III according to the serum creatinine value at 72 hours.

Serum creatinine detected 56% of patients with early AKI at 24 hours after snake bite. It showed that 44% of patients there was no AKI at 24 hours after snake bite. This shows the drawback of Serum creatinine such that it does not increase until the GFR has decreased moderately. Serum creatinine production varies according to muscle mass, age, gender and dietary factors. Tubular secretion contributes approximately 20% of total creatinine excretion and it can increase as GFR decreases. Creatinine blind area (40–70ml/min/1.73 sq m) gives a false security and late detection of kidney damage.

Serum cystatin C detected 94% of patients with early AKI at 24 hours after snake bite. It showed that 6% of patients there was no AKI at 24 hours after snake bite. There was a statistically significant positive linear correlation indicating that the fall in serum creatinine levels are reflected in serum cystatin-C levels as well.

About 20 participants (40%) who were not detected with early AKI by creatinine based e-GFR were detected as having early AKI by cystatin-C based e-GFR. This shows the advantage of cystatin C such as it is not affected by gender, age, muscle mass and protein intake. Cystatin C increases proportionately as GFR decreases and it is an ideal endogenous marker of GFR. Serum cystatin C is a better marker of renal function in early stages of AKI. Serum cystatin C based GFR is more accurate and useful for early intervention which results in a favorable outcome.

References

1. Schneemann MR, Cathomas ST, Laidlaw AM, El Nahas RDG, Theakston, Warrell DA. Life-threatening envenoming by the Saharan horned viper (*Cerastes cerastes*) causing microangiopathic haemolysis, coagulopathy and acute renal failure: clinical cases and review. 2004. 97(11):717-27.
2. Osler W. Acute bright's disease. The principles and practice of medicine: Designed for the use of practitioners and students of medicine. 2nd ed. Michigan, D: Appleton and Company. 1912; Pp. 743-56.
3. Daley BJ. Jun 7, 2012. Snakebite. eMedicine, Medscape.com.
4. Aurebch SP, Norris LR. Disorders caused by reptile bites and marine animal exposures. 18th ed. Chapter 391. In: Harrison's principles of internal medicine, New York: McGraw-Hill Mechanical Publishing Division; 2008 pp. 2741 & 2743.
5. Warrel DA. Guidelines for the management of snakebites. WHO Cataloguing in Publication Data. 2010; ISBN 978-92-9022-377-4.
6. Kardong KV. The evolution of venom apparatus in snake from Colubrids, Viperids and Elapids. *Mem Inst Butantan* 1982; 46:105-18.
7. Frangides CY. Snake venom poisoning in Greece. Experiences with 147 cases. *European Journal of Internal Medicine* 2006; 17:24-7.
8. Livia SR, Glória Elisa MF, Carla CP, Emmanuel BA. Acute kidney injury caused by Bothrops snake venom. *Nephron Clin Pract* 2011; 119:131-7.
9. R. Kumaresan. Is cystatin C estimation a better marker in chronic kidney disease patients? *International Journal of Pharma and Bio Sciences*.
10. Harrison's principles of internal medicine 18th edition. Acute kidney injury; New York: McGraw-Hill Mechanical Publishing Division; page 2293-2308.
11. Brenner and Rector kidney 7ed. Acute renal failure chapter 27.
12. Hilde R, H. De Geus¹, Michiel G. Betjes² and Jan Bakker. Biomarkers for the prediction of acute kidney injury: a narrative review on current status and future challenges; *Clin Kidney J*. 2012; 5: 102-108.
13. Won K, Han. Biomarkers for early detection of acute kidney injury; www.nephrologyrounds.org. 6 (4).

14. Qing-ping wang, jian-wen gu, xiang-hong zhan, hui li and xiang-hang luo.. assessment of glomerular filtration rate by serum cystatin c in patients undergoing coronary artery bypass grafting *ann clin biochem.* 2009; 46: 495
15. Kellum aj, unruh lm, murugan r. Acute kidney injury. *Bmj publishingJournal group ltd clinical evidence.* 2011;3.
16. Wang herget-rosenthal s, marggraf g, husing j. Early detection of acute renal failure by serum cystatin c. *Kidney int.* 2004 ;66:1115-1122.
17. Qiang li, jie-yu fang.. Cystatin c and serum creatinine in estimating Acute kidney injury of shock patients; *world j emerg med.* 2010; vol 1, no 3.
18. Sean m. Bagshaw, rinaldo bellomo. Early diagnosis of acute kidney injury; current opinion in critical care. 2007, 13:638-644.
19. M.s.n.murty. Serum cystatin c as a marker of renal function in detection of early acute kidney injury July 2013; www.nephrology.org
20. Mi yeon chung1. Diagnostic value of cystatin c for predicting acute kidney injury in patients with liver cirrhosis; *the korean journal of hepatology* 2008;3:962-7.