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Original Research Article

A study on outcome of malaria and acute gastroenteritis induced acute kidney injury requiring hemodialysis

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ABSTRACT

Background: Acute kidney injury previously known as acute renal failure, is characterized by the sudden impairment of kidney function resulting in the retention of nitrogenous and other waste products normally cleared by the kidneys. Acute Kidney Injury is usually manifested as multiorgan failure syndrome and extracorporeal support may also target fluid overload and heart failure, extracorporeal CO_2 removal for combined kidney and lung support, albumin dialysis for liver support. Haemodialysis is more effective than peritoneal dialysis for management of Acute Kidney injury as Peritoneal dialysis is associated with clearance limitation and difficulties with fluid removal and is thus rarely used in adults in developed countries.
Methods: The study was conducted in the Department of Medicine, Pt. J.N.M. Medical College and Dr. B.R.A.M. Hospital, Raipur (CG), India, from 2010 to 2012. All patients of both the sexes who were diagnosed as a case of Acute Kidney Injury due to Acute Gastroenteritis and Malaria and who were advised for Hemodialysis were included in the study. In our study, 32 patients of Acute Kidney Injury were included. The criteria used for AKI in the study was RIFLE criteria. Hemodialysis was done in all the cases. Quantitative variables are reported as means±SD and qualitative variables as percentage. Factor(s) determining outcome of AKI were tested by univariate analysis using "fisher's exact test". All variables with a P value <0.05 in the univariate analysis were defined statistically significant.
Results: Out of 32 patients of Acute Kidney Injury in our study, 50% (n=16) were of Malaria associated AKI cases and other 50% (n=16) patients were of Acute Gastroenteritis associated AKI in which 87.5% males,12.5% Females were of Malaria and 75% male,25% Female were in AGE associated AKI. Maximum number of patients presented with features of AKI within first 3days of disease onset i.e. 56.25% (n=9) of malaria patients and 68.75% (n=11) of AGE patients. Mortality due to MOD was more common in Malaria patients as compared to AGE patients. AGE associated AKI patients had different level of deranged SOFA score.
Conclusions: Acute kidney injury due to acute gastroenteritis differs from other causes of AKI by frequent occurrence of hypokalemia. Early diagnosis and prompt management can restore the kidney function.

Keywords: Acute kidney injury, Acute gastroenteritis, Malaria, SOFA score

INTRODUCTION

Acute kidney injury previously known as acute renal failure, is characterized by the sudden impairment of kidney function resulting in the retention of nitrogenous and other waste products normally cleared by the kidneys.It is characterised by an increase in the blood urea nitrogen concentration and/or an increase in the plasma or serum creatinine concentration, often associated with a reduction in urine volume.[1,2]

Acute tubular necrosis is the most frequent cause of acute kidney injury in which Prerenal azotemia is the most common manifestation. It is observed that Malaria and

Acute gastroenteritis are the most common cause of prerenal Acute kidney injury.[3,4]

Malaria itself is not associated with much of complication. Acute Kidney injury the most dreaded complication that occurs in *P. falciparum* malaria in less than 1% of cases, but the mortality in these cases may be up to 45%. It is more common in adults than children.[5]

About 500 million people suffer from malaria, leading to death in 1 to 3 million cases. The overall prevalence of Acute kidney injury in *falciparum malaria* varies between <1 and 60%. It occurs commonly in *Plasmodium falciparum* malaria and rarely in *Plasmodium vivax* malaria. In falciparum malaria the prevelance of mortality rate in multiorgan failure is up to 45% which may be 6.4% in one or fewer organs failure and increases to 48.8% with failure of two or more organs.[6]

Gastroenteritis is also an important cause of acute kidney injury. It was reported that gastroenteritis as a cause of acute kidney injury in 22-44.5% of the cases.[7]

Diarrhoea is the passage of 3 or more loose or liquid stools per day, or more frequently than is normal for the individual. It is defined as passage of abnormally liquid or unformed stools at an increased frequency, stool weight >200 g/d. This is defined as the passage of three or more than three loose or watery stool in 24 h, or passage of one or more bloody stool. Gastroenteritis results in acute tubular necrosis and renal failure if it hypovolemia is not corrected in time.[8]

It was estimated that about 4 billion cases of diarrhea occurred worldwide, resulting in 2.5 million deaths in 1996. An estimated 4.6 billion cases of diarrhoeal illness occurred worldwide in 2004, causing 2.2 million deaths, 1.5 million of which were in children. Acute kidney injury was known cause of death in 6.8% cases of acute gastroenteritis. It was estimated that renal failure accounts for 6.5% cause of death in acute gastroenteritis of which acute kidney injury occurred in 3.5%.[9]

Acute kidney injury is usually manifested as multiorgan failure syndrome and extracorporeal support may also target fluid overload and heart failure, extracorporeal CO2 removal for combined kidney and lung support, albumin dialysis for liver support.[10]

Haemodialysis is more effective than peritoneal dialysis for management of acute kidney injury as Peritoneal dialysis is associated with clearance limitation and difficulties with fluid removal and is thus rarely used in adults in developed countries. It may be useful when hemodialysis is unavailable or if vascular access is inaccessible.

Therefore, this study has been done to evaluate outcome of Malaria and Acute Gastroenteritis induced Acute Kidney Injury.

METHODS

The study was conducted in the Department of Medicine, Pt. J.N.M. Medical College and Dr. B.R.A.M. Hospital, Raipur from 2010 to 2012. All patients of both the sexes who were diagnosed as a case of acute kidney injury due to acute gastroenteritis and malaria on the basis of clinical history, examination, biochemical markers, and who were advised for Hemodialysis were included in the study.

In our study, 32 patients of acute kidney injury were included. Acute kidney injury for the purpose of study included:

- Malaria associated acute kidney injury 16 patients
- Acute gastroenteritis associated acute kidney injury 16 patients

Criteria for the diagnosis of acute kidney injury

The diagnosis of acute kidney injury was used when there was evidence of kidney injury in some clinical settings without prior history of any Kidney disease. The term acute kidney injury was used when there was rise in Serum creatinine ≥44 µmol/L (≥0.5mg/dL) along with the history of decreased urine output of less than 0.5ml/kg/hr for more than 6hrs.

The criteria used for AKI in the study was RIFLE criteria (given by Acute Dialysis Quality Initiative Group 2004) and is as follows.[2]

Table 1: Illustrating RIFLE criteria.

Class	GFR criteria	Urine output criteria
R-Risk I-Injury F-Failure L-Loss E-ESRD	Creatinine increase x1.5 or GFR loss>25% Creatinine increase x 2 or GFR loss>50% Creatinine increase x 3 or GFR loss>75% Persistent loss of kidney function>4wks ESRD >3months	<0.5 ml/kg/hour>6hrs <0.5 ml/kg/hour>12hrs <0.3 ml/kg/hour>24hrs Or anuria > 12hrs

Diagnosis of cause of acute kidney injury

There are many causes of acute kidney injury of which we used acute gastroenteritis and Falciparum malaria in our study.

- Acute Gastroenteritis- History of Passage of abnormally liquid or unformed stools at an increased frequency stool weight >200 g/d <2 weeks in duration.
- Falciparum Malaria- Positive test for Falciparum Malaria either by an

Patients having following criteria were excluded from the study:

- Severe active GI bleeding
- Renal Failure caused by end-stage malignant tumour
- Intracranial haemorrhage and intracranial hypertension
- Patients who cannot stand the extracorporeal circulation due to Coronary insufficiency or severe Arrhythmias
- Uncontrolled diabetes mellitus
- Other causes of jaundice like hepatitis, obstructive jaundice.

Patients of Falciparum malaria and acute gastroenteritis having acute kidney injury who were indicated for Hemodialysis, advised by treating physician and fulfilled inclusion and exclusion criteria were selected for study purpose.

Patients were assessed to follow criteria of Acute kidney injury after subjecting to detailed history and investigations. Hemodialysis was done in all the cases. The severity of illness was assesed using Glassgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA) score, Multiorgan dysfunction scores (MODS). These scales and scores help in assessing prognosis and outcome of the patients in study.

Statistical analysis

Quantitative variables are reported as means±SD and qualitative variables as percentage. Factor(s) determining outcome of AKI were tested by univariate analysis using "fisher's exact test". All variables with a P value <0.05 in the univariate analysis were defined statistically significant.

RESULTS

Out of 32 patients of acute kidney injury in our study, 50% (n=16) were of malaria associated AKI cases and other 50% (n=16) patients were of acute gastroenteritis associated AKI in which 87.5% males,12.5% females were of malaria and 75% male, 25% female were in Age associated AKI. Sex wise analysis revealed that males (n=26) predominated over females (n=6) with a male to female ratio of 4.3:1. Also the incidence of malaria is distinctly more in males (87.5%) than in females (12.5%) (Table 2).

Table 2: Sex distribution of cases of malaria and age associated AKI.

	Male	%	Female	%
Malaria associated AKI	14	87.5	2	12.5
AGE associated AKI	12	75	4	25

In present study3.12% patients of AKI patients fall in less than 10 years age group while 15.62 % of patients are above in 11-20 yrs of age group. 18.75 % patients are of 21-30 years group, 28.12% in 31-40 years age group, 31.25% in 41-50 years age group, 3.12% in >50 year age group. The patients of AKI was more in 11-50years age group, however it was maximum in 41-50 year age group (31.25%) (Table 3).

Table 3: Age distribution among patients of AKI.

Age in years	No	%
<10	1	3.12
11-20	5	15.62
21-30	6	18.75
31-40	9	28.12
41-50	10	31.25
>50	1	3.12
Total	32	100

As was expected fever and diarrhoea were major presenting complaints in malaria and AGE respectively present all 16 patients (100%). Vomiting was present in 50% (n=8) patients of malaria associated AKI and 83.33% (n=13) patients of AGE. Jaundice was present in 18.75% (n=3) patients of malaria associated AKI group. Decreased urine output occurred in all the patients. Pedal edema was present in 31.25% (n=5) patients of each group.

Table 4: Major presenting complaints and interval between disease onset and development of AKI among study subjects.

Presenting complaints	Malaria (N=16)		Age (N=16)	
	No.	%	No.	%
Fever	16	100	2	16.667
Jaundice	3	18.75	0	0
Decreased urine output	16	100	16	100
Vomiting	8	50	13	83.33
Pedal Edema	5	31.25	5	31.25
Diarrhoea	0	0	16	100
NO. OF DAYS				
1-3	9	56.25	11	68.75
4-6	3	18.75	5	31.25
7-9	4	25	0	0
Total	16	100	16	100

Maximum number of patients presented with features of AKI within first 3 days of disease onset i.e. 56.25% (n=9) of malaria patients and 68.75% (n=11) of AGE patients. 18.75% (n=3) of malaria and 31.25% (n=5) of age patients developed AKI in 4-6 days interval and 25% (n=4) malaria patients presented after 7days. Mean interval between disease onset and development of AKI is 4.125 + 2.6 days for malaria group and 3.0 + 1.59 days. The Interval between disease onset and development of

AKI is observed within first 3days in most of the cases of study group (Table 4).

Table 5: Number of patients having deranged LFT and hematological derangement.

Disease	Deranged LFT	Decreased platelet count	Decreased hemoglobin
Malaria	2 (12.5%)	10 (62.5%)	11 (68.75%)
AGE	3 (18.75%)	6 (37.5%)	8 (50%)

Malaria associated AKI patients having deranged LFT were 12.5% while age associated AKI were 18.75%. 62.5% % (n=10) malaria patients had decreased platelet count while 68.75% (n=11) malaria patients had decreased Hemoglobin, while 37.5% of age patients had decreased Platelet count and 50% had decreased Hemoglobin. So, it can be concluded that haematological derangement was more common in Malaria associated AKI (Table 5).

Table 6: Number of patients having electrolyte imbalance.

	Malaria		Age	
	No. of patients	%	No. of patients	%
Na+ Imbalance	3	18.75	6	37.5
K+ Imbalance	4	25	3	18.75

Out of 16 Malaria patients 18.75% (n=3) had sodium imbalance, while 25% (n=4) had potassium imbalance. In age associated AKI patients' sodium and potassium imbalance occurred in 37.5% (n=6) and 18.75% (n=3) respectively (Table 6).

Table 7: Number of patients requiring ventilator support.

Disease	Total no. of patients	Patient with ventilator support	%
Malaria	16	3	18.75
Age	16	2	12.5

Out of 32 patients 5 patients (31.25%) required ventilator support, out of which 18.75 % (n=3) patients were of Malaria while 12.5% (n=2) were of age. The requirement of Ventilator support was more in Malaria as compared to AGE patients in present study (Table 7).

Out of 16 Malaria associated AKI patients 2 (12.5%) required 1 HD, 7 (43.75%) required 2HD, 2 (12.5%) required 3 HD, 5 (31.25%) required ≥4 HD. Mean of 2.68+1.2. Out of 16 AGE associated AKI patients 2 (12.5%) required 1 HD, 7 (43.75%) required 2HD, 4 (25%) required 3 HD, 3 (18.75%) required ≥4 HD. Mean of 2.75+1.5. Maximum no. of patients in present study required ≥2 hemodialysis. Out of 16 Malaria associated AKI patients 1(6.25%) patients required 5 days hospitalization, 4 (25%) patients required 7-9 days, 11 (68.75%) required >10 days. Mean of 11.25+3.45 days of hospitalization was required. Out of 16 age associated AKI patients 4 (25%) patients required 4-6 days, 3 (18.75%) patients required 7-9 days, 9(56.25%) required >10 days. Mean of 9.9+3.6 days of hospitalization was required (Table 8).

Table 8: Number of sessions of haemodialysis required and days of hospital stay among study subjects.

	Malaria		Age	
	No.	%	No.	%
No. of sessions of HD				
1	2	12.5	2	12.5
2	7	43.75	7	43.75
3	2	12.5	4	25
>4	5	31.25	3	18.75
Number of days of hospital stay				
1 to 3	0	0	0	0
4 to 6	1	6.25	4	25
7 to 9	4	25	3	18.75
>10	11	68.75	9	56.25

Out of 16 malaria associated AKI patients 50% (n=8) had single organ dysfunction in which none of the patient died while 50% (n=8) had multiorgan dysfunction of which 2 (25%) expired. Out of 16 malaria associated AKI patients 50% (n=8) had single organ dysfunction in which one (12.5%) died while 50% (n=8) had multiorgan dysfunction of which 2 (25%) expired. Mortality due to MOD was more common in Malaria patients as compared to age patients. AGE associated AKI patients had different level of deranged SOFA score (Table 9).

Table 9: Patients having single organ damage (SOD) and multiple organ damage (MOD) in cases of malaria and age.

	Malaria			Age		
	No. of patients	Mortality	%	No. of patients	Mortality	%
SOD	8	0	0	8	1	12.5
MOD	8	2	25	8	2	25
Total	16	2		16	3	

After dialysis 87.5% (n=14) malaria associated AKI patients survived, while 81.25% (n=13) age associated AKI survived after dialysis. Out of 5 patients who did not survived, 2 were of post malaria AKI and 3 were of post age AKI group (Table 10).

Table 10: Number of survivors and non-survivors.

	Malaria associated AKI		AGE associated AKI		Total
	No.	%	No.	%	
Survivors	14	87.5	13	81.25	27
Non-Survivors	2	12.5	3	18.75	5
	16	100	16	100	32

DISCUSSION

In present study sex analysis revealed that males (81.25%) predominated over females (18.75%) with a male to female ratio of 4.3:1. While in study done by Feest TG et al 125 adults patients of acute renal failure, 90 males (72%) and 35 (28%) females were present, the ratio being 2.5:1.[11]

Prakash J et al in their study including 26 patients having Falciparum Malaria 19 were males (73%) and 7 (27%) were females.[12] In Study done by Kute VP et al Malaria associated AKI 74.5% were males and 24.5 % were females.[6]

Carneiro I et al in their study mentioned that severity of Malaria correlates with age, it is associated with most severe complications in the younger age group which is nearly similar to the finding of the present study.[13]

In malaria associated AKI patients presenting complaints were fever in 100 % males and females; jaundice occurred in 21.4% males only; decreased urine output occurred in all the patients; vomiting occurred in 50% of males and 50% of females; pedal oedema occurred in 28.5 % of males and 50% of females in present study. The occurrence of vomiting most often coincided with the occurrence of diarrhoea.

As per the result of Barsoum RS jaundice is the most common association with malarial ARF (MARF), occurring in more than 75% of cases.[14]

As in present study, fever was present in 100% in 124 patients of malaria due to AKI in study done by Naqvi R et al 2003; similarly, 100% patient had fever in a study involving 200 patients by Panwar S et al.[15, 16]

In study by Wasnik PN et al in 80 confirmed cases of Falciparum malaria fever was the most common symptom observed in all patients and majority of patients presented in the hospital within a week of onset of symptoms.[17]

AGE patients presented with diarrhoea (75% males and 75% females) vomiting (83.33% males and 75% females), fever (16.67% males only), decreased urine output (100% males and females), pedal oedema (33.33% males and 25% females).

Out of 16 malaria associated AKI patients 1 (6.25%) patients required 5 days hospitalization, 4 (25%) patients required 7-9 days, 11 (68.75%) required >10 days. Mean of 11.25+3.45 days of hospitalization was observed in present study.

Out of 16 age associated AKI patients 4 (25%) patients required 4-6 days, 3 (18.75%) patients required 7-9 days, 9 (56.25%) required >10 days. Mean of 9.9+3.6 days of hospitalization was observed in our study.

In a study done by Clermont G et al, in which 254 AKI patients admitted in ICU were included and the mean day of Hospital stay was 11+1.[18]

From present study it was concluded that patients with MOD had longer stay in the hospital similar observation was made by Liangos O et al 2006 who demonstrated the increased days of stay in hospital of patients with MOD.[19]

Length of ICU stay was 3.7±4.7 days for AKI patients in study done by Janssens U et al.[20] The cause of longer stay in our setting was presence of multiorgan dysfunction, which prolongs the course of illness.

Out of 16 malaria patients 18.75% i.e. 3 patients had sodium imbalance, while 25% (4) patients had potassium imbalance, while in age sodium and potassium imbalance occurred in 37.5% and 18.75% respectively.

Hyponatremia, usually asymptomatic, is observed in 71% (n = 42) of the patients. Hyponatremia in adults with severe malaria is common and associated with preserved consciousness and decreased mortality. It likely reflects continued oral hypotonic fluid intake in the setting of hypovolemia and requires no therapy beyond dehydration.[6]

Hyponatremia is a common complication of AKI due to absolute or relative increase in free water intake. It was 28.12% (n=9) in present study compared to 19% in study by Anderson et al. This is because of loss of sodium from body through diarrhoea and vomiting.[21]

Hypokalemia is a minor and unusual complication during recovery phase of AKI. In present study it was present in 15.6%. Hyperkalemia is common complication of AKI but was seen in 6.25 % in present study as compared to 75 % in the study conducted by Minuth et al 1976, so from study it can be concluded that hypokalemia is a major complication than hyperkalemia in AKI patients. [22]

Malaria associated AKI patients having deranged LFT in the form of increased serum bilirubin, increased serum

enzymes were 12.5% while AGE AKI associated were 18.75%. While in study by Kute VB et al 75% Malaria associated AKI patients had deranged LFT. [6] Naqvi R et al showed 50% patients having deranged LFT in their study involving 124 malaria associated AKI patients. [15]

Out of 32 patients 5 patients (31.25%) required ventilator support, out of which 18.75 % i.e. 3 patients were of Malaria while 12.5% were of AGE, mortality in patients who required ventilator support was 100% so it can be concluded that this might be a significant prognostic factor for mortality, as was also noticed in the study done by Uchino S et al 2005 in which the mortality was 95% in patients having ventilator support, so it can be regarded as an independent prognostic factor for mortality in AKI patients. [23]

Contrary to present result was seen in a study done by Lobo SM et al only 58% of ARF patient required ventilator support. [24] Out of 16 Malaria associated AKI patients 2(12.5%) required 1 HD, 7(43.75%) required 2HD, 2 (12.5%) required 3 HD, 5(31.25%) required ≥4 HD. Mean of 2.68+1.2 HD was required in our study. While in study done by Kute V B et al 2012 the mean of HD required was 4.54 +3.03. [6] The mean no. of dialysis in the study done by Wilairatana P, et al for malarial ARF was 6.5 (range = 1-27). [25]

Out of 16 AGE associated AKI patients 2(12.5%) required 1 HD, 7(43.75%) required 2HD, 4(25%) required 3 HD, 3(18.75%) required ≥ 4 HD. Mean of 2.75 + 1.5 HD was required in our study.

After Dialysis 87.5 Malaria associated AKI patients survived, while 81.25 AGE associated AKI survived after dialysis in the current study. While in study done by Kute V B et al 2012 91.23% malaria associated AKI patients survived.[6] Mortality of malaria associated AKI who received RRT was 37% in a study done by Hanson J et al.[26]

In a study by Schiffl H et al the overall mortality among all patients enrolled for haemodialysis was 37 percent (59 of the 160 patients died). [27] AKI has 46.5% mortality and the most frequent causes of death were sepsis, respiratory failure and multiple organ failure. ARF is an important marker of the gravity of the underlying disease and not the cause of death, so crucial part of present studyis to determine the involvement of multiple organs in present studygroup to assess the prognosis and outcome. [28]

Out of 16 Malaria associated AKI patients in present study12 i.e. 75% had single organ dysfunction while 4 i.e. 25% had Multi organ dysfunction in which mortality was 50% in patients with Multi organ dysfunction.

Only 11 of 172 patients with one or no organ failure died (6.8%), whereas mortality rate increased to 48.8% in 129 patients with multiple organ failure in the study by Krishnan A et al 2003. [29]

In a study done by Wasnik PN et al 46.25% of 81 Malaria patients had multiple organ involvement.[17]

Mortality rate was 6.4% in single organ failure, and increased to 48.8% with failure of two or more organs in the study done by Kute VB et al in 50 Malaria associated AKI patients.[6] Therefore it can be concluded that multiple organ involvement is the major determinant of mortality in AKI patients.

As per present study 22.5% (n=14) mortality was seen in Malaria associated AKI Patients among 16 patients of present study group, while in a study done by Nadkar M Y et al 2012 in 223 patients of Falciparum malaria mortality was 16.4 % (n=36).[30] Prakash J et al concluded in their study 20% (n=19) among 95 Malarial ARF patients. [12]

CONCLUSION

Acute kidney injury due to acute gastroenteritis differs from other causes of AKI by frequent occurrence of hypokalemia. In comparison to Acute kidney injury due to acute gastroenteritis, acute kidney injury due to Malaria was associated multiorgan dysfunction in most of the patients. Early diagnosis and prompt management (like fluid replacement, correction of electrolyte abnormality, administration of appropriate antibiotics, Hemodialysis) can restore the kidney function.

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