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CLINICAL STUDY OF ACUTE KIDNEY INJURY IN HIV INFECTED AND HIV UNINFECTED PATIENTS.

Medicine

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ABSTRACT

Acute kidney injury (AKI) is abrupt decline in renal function, defined by increase in serum creatinine and /or reduced urine output. AKI in HIV patients is associated with opportunistic infections, drugs and immunosuppression. Although there are number of studies in relation with AKI in HIV infected and HIV uninfected patients, there is lack of comparative data.

We studied first 30 HIV infected and 30 HIV uninfected patients admitted with AKI in medicine ward of a tertiary hospital, divided in two groups on the basis of HIV Elisa report. Patients with underlying chronic kidney disease were excluded. Data regarding etiological factors, clinical presentation, laboratory investigations, treatment given and their outcome at 1 week and 3 month later was noted and compared.

Among the HIV negative patients, 25(83.33%) had pre-renal, six(20%) had renal, and four(13.33%) had post-renal cause. Whereas, among the HIV positive patients 13(43.33%) had pre-renal, 18(60%) had renal and five(16.66%) had post-renal cause. Some of these patients had overlap of pre renal and renal or renal and post renal causes.All 18 patients with renal AKI were on Tenofovir disoproxilbased regimen. All (7)HIV patients who died had CD4 less than 300cells/mm3. Median CD4 in survivors was 309cells/mm3 and in patients who died was 129cells/mm3. The two groups were comparable with respect to age and sex distribution, clinical features, creatinine levels and outcome. AKI in HIV patients is most commonly associated with infections and drugs. Low CD4 count is associated with poor outcome of AKI. However, large randomised studies are needed to determine the association between anti-retroviral drugs and AKI.

KEYWORDS

AKI, CD4, Tenofovir, HIV.

INTRODUCTION-

Acute kidney injury (AKI) is characterized by abrupt deterioration in kidney function, manifested by rise in serum Creatinine levels or reduction in urine output. Kidney Disease Improving Global Outcomes (KDIGO) defines AKI as any of the following1:

Increase in serum creatinine by 0.3mg/dL or more within 48 hours or Increase in serum creatinine to 1.5 times baseline or more within the last 7 days or Urine output less than 0.5 mL/kg/h for 6 hours The diagnostic evaluation can be used to classify acute kidney injury as pre-renal, intrinsic/renal, or post-renal. Some aetiologies are common to both HIV infected and HIV uninfected patients, the prognosis is usually worse in patients with HIV2. HIV infection in itself or the medications used for treatment of HIV and diseases associated with it have been increasingly recognized to cause renal failure associated with HIV3,4,5. AKI in HIV has been associated with lower CD4 cell counts, higher HIV RNA level, HCV co-infection, history of Antiretroviral therapy (ART) exposure and opportunistic infections6,7. Clinical presentation8,9,10,11,12 varies with the cause and severity of renal injury, and associated diseases. Most patients with mild to moderate acute kidney injury are asymptomatic and are identified on laboratory testing. Patients with severe cases, however, may be symptomatic and present with listlessness, confusion, fatigue, anorexia, nausea, vomiting, weight gain, or oedema. Some of the patients present with complications like acidosis, hyperkalaemia and encephalopathy. Patients can also present with oliguria (urine output less than 400 mL per day), anuria (urine output less than 100 mL per day), or normal volumes of urine (non-oliguric acute kidney injury)10,11. Management of AKI involves fluid resuscitation, avoidance of nephrotoxic medications and contrast media exposure, and correction of electrolyte imbalances and renal replacement therapy (dialysis). Recognition of risk factors (e.g., older age, sepsis, hypovolemia/ shock, cardiac surgery, infusion of contrast agents, diabetes mellitus, pre-existing chronic kidney disease, cardiac failure and liver failure) is important13. Prognosis in AKI varies with severity and aetiology. Prognosis is usually worse in patients of intensive care unit. AKI is associated with poor health outcomes in HIV-infected patients. By doing this study, we planned to study and compare the clinical manifestations, aetiology and outcome of AKI in HIV infected and HIV uninfected patients.

METHODS-

We selected first 30 PLHIV and 30 HIV uninfected patients aged more than 12 years admitted in the medicine ward of a tertiary general hospital in the state of Maharashtra, India over a period of six months from December 2014with acute kidney injury defined as any one of the following-

1. s. creatinine > 3mg/dl
2. 1.5 fold rise in s. creatinine from baseline
3. Urine output < 0.5ml/kg/hr for more than 12hrs.

We excluded any patient who was suspected to have acute kidney injury with underlying chronic kidney disease. Patients who gave a written informed consent for the study were included. These patients were divided into two groups on the basis of HIV ELISA report of the patient into HIV infected and HIV uninfected. Patients were not age or sex matched. Demographic details, chief complaints and relevant negative history were recorded for each patient. Past History, Obstetrical History, Menstrual history, Personal History, Family History was recorded. Detailed clinical examination of every patient was done to note etiological factors, clinical manifestations and treatment given in each patient. Patients were followed one week and three month later to determine the outcome. Every patient underwent the following investigations- Complete blood count, serum creatinine by Jaffe method,serum urea by urease method, serum electrolytes, total bilirubin levels, alanine transaminase, aspartate Transaminase, alkaline phosphate, serum uric acid,blood sugar level, arterial blood gas analysis, HIV elisa, CD4 count (HIV positive patients), Urine-routine and microscopic examination,24 hour urine protein an ultrasound of abdomen. Serum creatinine and Urea were rechecked one week and three months later in all patients to determine their residual renal function. Ethics Committee of Medical College approved the study. We reported our analysis in terms of frequencies, proportions, medians, bar diagrams and used chi-square test and ANOVA for comparisons.

RESULTS:

Table 1. Table showing the results obtained for both the groups and their p values

	PLHIV	HIV Uninfected	P Value
Age (mean)	38 yrs	42 yrs	0.31
Sex	Female-53.33% Male- 46.66%	Female- 46.66% Male- 53.33%	0.8
Etiology	Pre-renal- 43.33% **Renal- 60%** Post-renal- 16.66%	Pre-renal- 83.33% **Renal- 20%** Post-renal- 13.33%	0.036 **0.001** 0.7

Clinical Features			
Dehydration	56.66%	46.66%	
Edema	20%	33.33%	0.38
Oliguria/ anuria	73.33%	83.33%	0.33
Complications			
Acidosis	46.66%	30%	
Hyperkalemia	23.33%	26.66%	0.29
Encephalopathy	10%	26.66%	1
Creat on admission	Mean- 3.12	Mean- 3.23	0.85
Creat at 1 week	Mean- 2.6	Mean- 3.07	0.41
Creat after 3 months	Mean-1.05	Mean- 1.15	0.67
Hemodialysis	30%	36.66%	
Mortality	23.33%	13.33%	0.5

Of the total of 60 patients studied, 36 patients belonged to the age group of 20-40. All the HIV positive patients were less than 60 years old. However, there were four patients who were older than 60 years among the HIV negative patients. The mean age in HIV positive group was 38 years and the mean age in HIV negative group was 42years. There were 14(46.66%) female and 16(53.33%) male patients in HIV negative group, and 16(53.33%) female and 14(46.66%) male patients in the HIV positive group.

On assessing the history and clinical presentation, among the HIV negative patients, 25 patients were determined to have developed AKI due to pre-renal cause (on the basis of history and examination suggestive of decreased volume Table 1 showing demographic and clinical the results obtained for both the groups and their p values

status or renal perfusion and which responded to improved perfusion), six had renal cause, and four had post-renal cause suggested by an obstructive pathology of urinary tract. Whereas, among the HIV positive patients only 13 patients had pre-renal, 18 had renal and five patients had post-renal cause. There was a likely overlap of aetiology in 9 patients. P value for renal cause was 0.001 and for pre-renal cause was 0.036, hence found statistically significant. P value for post-renal cause was 0.7 and hence not significant. All HIV positive patients with renal AKI, a total of 18, had history of Tenofovir disoproxilintake. (Figure 1)

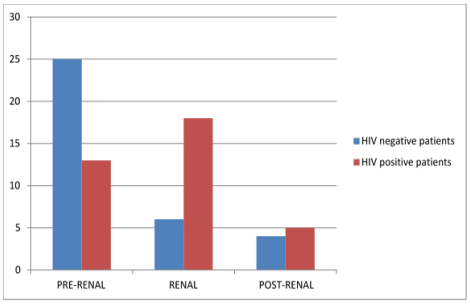

Figure -1 showing the distribution of patients as per aetiology in HIV negative and HIV positive patient groups.

Among the HIV negative patients who developed AKI due to pre-renal cause, eight had AGE, six had Hypovolemia due to other causes like blood loss during delivery, inadequate intake etc.; eight developed AKI associated with liver injury, two patients had sepsis, one patient had history of snake bite.

Among the HIV positive patients who developed AKI due to pre-renal cause, nine had AGE and four had sepsis (figure 2).

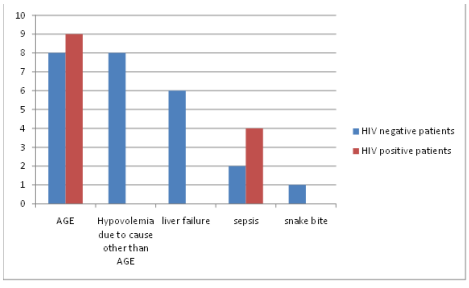

Figure 2 shows aetiological distribution of pre-renal AKI in HIV negative and HIV positive patients.

On studying the clinical manifestation we found that nine i.e. 30% HIV negative patients had icterus, of which five had alcohol related liver injury, two patients had pregnancy related jaundice, one had budd-chiari syndrome. None of the HIV positive patient had icterus.

We found that oedema was more common in HIV negative 10(33.33%) than HIV positive patients six (20%) but the difference was statistically insignificant.

Our study showed that 26 (83.33%) HIV negative and 22 (73.33%) HIV positive patients presented with either oliguria or anuria. This proportion was statistically similar.

While evaluating for complications we found that, nine (30%) HIV negative patients developed acidosis at some point in their illness and 14(47%) HIV positive had acidosis. However this difference was not statistically significant.

Out of 30 HIV negative patients, eight (26.66%) had hyperkalaemia at some point in their illness while among HIV positive patients, seven (23.33%) had hyperkalaemia. The difference was statistically insignificant.

It was found that uremic encephalopathy was prominent in HIV negative patients (26.66% of HIV negative patients versus 10% of HIV positive patients), however the difference was statistically insignificant.

In our study, 27 patients had CD4 below 500cells/mm3, whereas 18 patients had CD4 less than 300cells/mm3. All patients who died had CD4 less than 300cells/mm3. And six out of seven patients who died had CD4 less than 200cells/mm3. Median CD4 in patients who survived was 309cells/mm3 and in patients who died was 129cells/ mm3. This difference was found statistically significant.(figure 3 and 4)

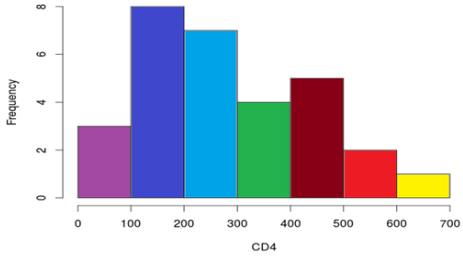

Figure 3 Histogram showing distribution of HIV positive patients with respect to their CD4 count

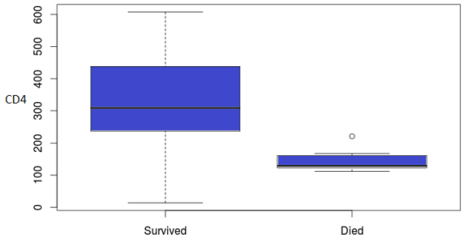

Figure 4 box and whisker plot demonstrating CD4 count in HIV positive patients who survived and HIV positive patients who died. Median CD4 in patients who survived was 309 and in patients who died was 129

Serum creatinine levels on admission were similar in both groups.The mean Creatinine in HIV negative group was 3.23 and the mean value in HIV positive group was 3.12. Some of the patients had normal s. creatinine values on admission and they got deranged subsequently during the course of admission.

Serum Creatinine level after one week was similar in both groups. The mean value was 3.07 for HIV positive patients and 2.6 for HIV negative patients.

Serum Creatinine levels after three month was also similar in both groups. The mean value for HIV positive patient was 1.05 and HIV negative patient was 1.15.

In our study, out of 30 HIV negative patients, 19(63.33%) were treated conservatively, of which one died and 11(36.66%) were hemodialysed

of which three died. Among the HIV positive patients, 21(70%) were treated conservatively and all survived, and 9(30%) underwent dialysis, of which seven died.

In our study mortality was higher in HIV positive patients, seven(23.33%) died among HIV positive patients, than in HIV negative patients, four(13.33%) patients died. But this difference in mortality was not statistically significant.

Among the30 HIV negative patients with AKI, two patients had persistently deranged RFT even after three month, four of them died, 26 survived with normal RFT. And among the HIV positive patients, one had persistently deranged Creatinine value, seven died and 22 survived with normal RFT (figure 5).

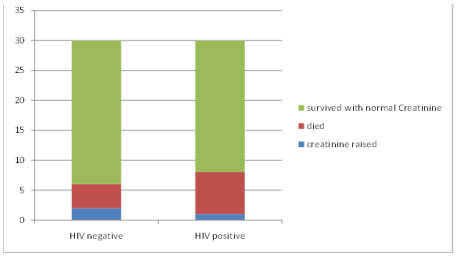

Figure 5 Shows outcome of patient at 3 month follow up in HIV negative and HIV positive patients.

DISCUSSION AND CONCLUSION

- In our study of the aetiology, clinical manifestations, treatment and clinical outcome of acute kidney injury in HIV infected and HIV uninfected patients, we observed that both the groups had similar distribution with respect to age and gender. Incidence of AKI was highest in the age group of 20-30 in HIV positive patients whereas it was highest in 30-40 years age group in HIV negative patients. In the study by Hari Janakiraman et al (2008) in 104 patients with HIV infection and renal involvement, the ages varied between 20 and 55 years with a median age of 33 years13.Pre-renal AKI was significantly more often seen in HIV negative patients than HIV positive patients. Renal AKI was significantly more often seen in HIV positive patients than HIV negative patients. All patients with renal AKI were on Tenofovirdisoproxil based regimen.History of nephrotoxic drug intake was significantly more in HIV positive than HIV negative patients, although causal association if any could not be ascertained.Of the 18 patients on Tenofovir disoproxil based regimen, 9 patients had an overlap of aetiology. This is similar to number of studies conducted in post HAART (highly active antiretroviral therapy) era in relation with AKI.In a Retrospective, non-comparative Study conducted by Horberget al, 238 patients treated by Tenofovirdisoproxil (TDF) was included. Significant increase of creatinine along the follow-up of 12 months (þ 0.1 mg/dl), P<0.005 was seen. Of these21% were diabetics, 17% were hypertensive, 18% had a baseline proteinuria, 5.5% had pre-existing renal pathologies,13% (29) were treatment naïve, 87% (209) were treated before. Median duration of TDF: 13 months14.Another prospective cohort study of 754 HIV patients, 18 years or older, was conducted at a university-based infectious disease clinic between 2000 and 2002. It was observed that AKI was more common in men, in those with CD4 cell count <200 cells/mm (3), and HIV RNA levels >10,000 copies/mL. These patients more often had acquired immunodeficiency syndrome (AIDS), hepatitis C infection (HCV), and have received HAART. AKI was mainly community-acquired, due to pre-renal causes or acute tubular necrosis, and associated with opportunistic infections and drugs. It concluded that AKI is common in ambulatory HIV patients and immunosuppression, infection, and HCV are important conditions associated with AKI in the post-HAART era15.

On studying the clinical manifestations, it was seen that majority patients in both the groups had oliguria, followed by dehydration, acidosis, oedema, hyperkalaemia, encephalopathy, and icterus. Acidosis and dehydration although more commonly seen in HIV positive patients than HIV negative patients, no statistical difference was found. Serum Creatinine range was similar in both the groups throughout the course of illness.

As six out of the seven HIV infected patients who died had CD4 below 200 while, all patients who died had CD4 count below 300, low CD4 count was associated with high mortality.Franceschini's study had also found that incidence rates of AKI were higher among patients with lower CD4 cell counts. And it also stated that CD4 count <200 cells/kl, remained an independent predictor of experiencing AKI16and the most important predictor of HIV-1-related morbidity and mortality. The higher mortality in patients who were dialysed was probably due to severity of the disease in the patients who were dialysed.A study was conducted by Gillum, Dixon et al regarding role of intensive dialysis in acute renal failure. It did not show any advantage of intensive dialysis in acute renal failure17.

AKI is associated with poor health outcomes in HIV-infected patients. In a cohort study18, in-hospital mortality of AKI in HIV-infected patients was 6-fold higher than seen in admissions of HIV-infected patients without AKI (27% vs.4.5%).Similarly, although statistically insignificant, mortality was higher in HIV infected patients than HIV uninfected patients in our study.

Our study showed significant differences with respect to etiological factors between both the groups but the two groups were statistically similar with respect to clinical manifestation, complications and outcome of AKI. Major limitation of our study is the small population. Large, randomised studies are needed to determine the ways in which AKI in HIV infected patients is different from AKI in HIV uninfected patients and relation of HAART with AKI in HIV patients.

There are no financial conflicts of interest to disclose.

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