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A HOSPITAL BASED PROSPECTIVE STUDY OF ACUTE KIDNEY INJURY IN CHILDREN WITH ACUTE GASTROENTERITIS AND ASSOCIATED RISK FACTORS

Paediatric Medicine

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ABSTRACT

Introduction: Acute kidney injury(AKI) is frequently under-estimated in children hospitalised for acute gastroenteritis(AGE).So,the detection of AKI and its risk factors can allow interception of patients who could be at risk of longer hospital stays and higher mortality and morbidity. In our study,we aimed to study proportion of children with AKI among those admitted with AGE and associated risk factors. **Methods:** This was an observational prospective study which included clinical and biochemical data of 131 children aged 6 months to 15 years hospitalized for acute gastroenteritis. Cases having previously known kidney disease, genetic syndrome or surgical abdomen were excluded. AKI was defined using KDIGO (Kidney Disease Improving Global Outcomes)staging.Categorical variables were analysed using chi-square test. Continuous variables were analysed using independent sample t-test. p-values ≤0.05 were taken as statistically significant. **Results:** AKI was found in 37/131 (28.2%) cases.Out of these,40.5% were in the age group of 6 months-2 years.Majority of cases(67.6%) presented in AKI stage 3. Longer duration of illness prior to hospitalisation, dehydration and hyponatremia were found to be significant risk factors(p≤0.05) for AKI. Duration of intravenous rehydration and length of stay were more in AKI cases (p=0.018 and 0.001 respectively).Renal replacement therapy was required in 37.8% cases with AKI.73% patients of AKI improved whereas 27% expired. **Conclusion:** About one-third of cases with AGE develop some form of AKI.Cases with longer duration of illness prior to hospitalisation,dehydration and hyponatremia should be paid particular attention as quick interventions can lead to improved outcomes.

KEYWORDS

Acute Kidney Injury, Acute Gastroenteritis, Children, Risk Factors

INTRODUCTION

Acute gastroenteritis (AGE) is among the leading causes of morbidity and mortality especially in developing countries like India, with 3-5 billion cases and around 2 million deaths occurring each year in children, mostly under 5 years of age[1].One of the most severe complications of acute gastroenteritis is acute kidney injury(AKI) which in most cases, is caused due to renal hypoperfusion,although other mechanisms can also be involved in few cases[2]. The prevalence of AKI is frequently under-estimated in children hospitalised for acute gastroenteritis especially in milder forms that are quickly reverted by rehydration. Hospitalized children who develop AKI could experience longer hospital stays and higher mortality in the short-term[3] and increased risk of chronic kidney disease (CKD), hypertension and proteinuria in the long-term[4-6]. In fact, even the milder forms of AKI can double the risk of CKD[6]. So, the detection of milder forms can allow interception of patients who could be at risk of the later. Few studies were conducted in western countries in this context but no study was conducted on Indian pediatric population in the past which took clinical and biochemical data into consideration. In our study, we aimed to evaluate the proportion of AKI and its risk factors in children hospitalised for acute gastroenteritis by means of direct access to clinical and biochemical data. So, our study is the first Indian study in this context.

METHODS

Clinical and biochemical data of children aged 6 months to 15 years consecutively hospitalised for acute gastroenteritis was collected in this observational prospective study conducted in Pediatric wards and Pediatric Intensive Care Units in Department of Pediatrics, SPNCHI, SMS Medical College & Hospital, Jaipur from June 2021 to August 2022.Inclusion criteria were the presence of at least one episode of vomiting and/or diarrhoea in the last 24 hrs before hospital admission and availability of basal serum creatinine levels at admission.We excluded children with previously known kidney disease, liver disease, heart disease, neurological disease, genetic syndrome, patiens with chronic diarrhoea,surgical abdomen and those who refused to give informed consent(Figure 1).This study was conducted after the approval by the Ethical Committee.

Data collection

Baseline clinical data on admission comprised demographic information, duration of symptoms before hospitalization, presence of loose motions, vomiting or both, fever, pain abdomen, abdominal distension, dysentery, cold extremities, dehydration(no, some, severe),blood pressure, Glasgow coma scale, urine output ,heart rate. Biochemical data on admission comprised serum urea, creatinine, sodium, potassium, chloride, calcium,bicarbonate and hematocrit. Baseline serum creatinine and creatinine clearance was determined at admission and then again, serum creatinine levels were done after 48 hrs and renal dysfunction was assessed using KDIGO (Kidney Disease Improving Global Outcomes) staging[7]. Serum creatinine levels were done by Jaffe's method.For patients without a prior baseline creatinine; an assumed creatinine clearance of 120 ml/min./1.73m2 was used.

Definitions

Acute Gastroenteritis(AGE) captures the bulk of infectious cases of diarrhoea. The most common manifestations are diarrhoea and vomiting, which can also be associated with systemic features such as abdominal pain and fever.[8]

Acute Kidney Injury was defined according to KDIGO guidelines[7] as any of the following:Increase in serum creatinine by greater than or equal to 0.3 mg/dl within 48hours, or increase in serum creatinine to greater than or equal to 1.5 times the baseline, which is known or presumed to have occurred within the prior 7 days or, urine volume less than or equal to 0.5ml/kg/hr for 6 hours.Both the creatinine and urine output criteria were used to define AKI.

Dehydration was classified as no dehydration, some dehydration and severe dehydration according to the World Health Organization (WHO)[9]definition which assesses the dehydration status according to some clinical parameters including general appearance (ranging from well to lethargic), eyes (normal or sunken), thirst (not thirsty, thirsty, drinks poorly, or not able to drink), and skin turgor (skin goes back quickly, slowly, or very slowly).Cases with no dehydration were the ones in well general condition, with normal eyes, not thirsty, and with skin that goes back quickly. Cases with two signs from among irritability, sunken eyes, thirsty, and skin turgor that goes back. slowly, were labelled having some dehydration. Cases with two signs from among unconscious or lethargic, sunken eyes, drinks poorly or not able to drink, and skin turgor that goes back very slowly were labelled severely dehydrated.

The Heart Rate(HR) was compared with percentiles for age and body temperature[10].Tachycardia was defined by HR > 2 standard deviation score (SDS).

Impairment of consciousness was defined as present or absent. We defined the impairment of consciousness as present in case of Glasgow coma scale < 15.

Sample Size

Sample size was calculated at 95% confidence level, alpha error of 0.05 expecting at least 5% dehydration as one of the risk factors for AKI in children hospitalized for acute gastroenteritis as per study by Marzuillo *et al*[11]. At 8% absolute allowable error, the required sample size was 131 cases of acute gastroenteritis admitted. This sample size was large enough to include all other variables and risk factors of AKI in acute gastroenteritis patient.

Statistical Analysis

The data collected regarding all the cases were entered in Microsoft Excel Sheet 2007.Categorical variables were expressed as frequency and percentage and were analysed using chi-square test. Continuous variables were expressed as mean and standard deviation and were analysed using independent sample t-test. A p-value of ≤0.05 was taken as statistically significant. All statistical analyses were done using Epi info version 7.2.1.0 statistical software.

RESULTS

Total 131 cases were enrolled after fulfilling the inclusion criteria. Age of children hospitalised with gastroenteritis included in this study ranged from 6 months-15 years. Mean age of cases was 4.10 ± 4.53 years. Most cases were aged below 2 years (47.3%).68 (51.9%) were males and 63 (48.1%) were females. The male : female ratio was 1.08 : 1. Among 131 cases, 37 (28.2%) cases developed AKI.Among the 37 cases with AKI, most cases[25(67.6%)] had AKI stage 3, while 8(21.6%) had AKI stage 1 and 4 (10.8%) had AKI stage 2. 40.5% of AKI cases were in the age group 6 months-2 years. However,no significant association was found between AKI and age and sex of cases (p=0.914 and 0.201 respectively). Most of the cases with AKI (i.e. 40.5% cases) had duration of illness >7 days before hospitalisation while in most of the non-AKI cases, duration of illness before hospitalisation was 1-3 days (42.6%).The difference in duration of illness before hospitalisation among AKI and non-AKI cases was found to be statistically significant (p<0.001). Most common clinical presentation among cases with AKI was fever and cold extremities, i.e. 86.5% ; however, the difference was not found to be statistically significant(p=0.732 and p=0.441 respectively). Out of 37 cases with AKI, 26 cases(70.3%) presented with dehydration(some dehydration or severe dehydration),while 11 cases(29.7%) presented with no dehydration. Significant association was found between AKI and hydration status of cases(p=0.056). Length of stay among most cases with AKI i.e. 59.5% cases, was 7-14 days, while among most non-AKI cases, i.e. 34% cases, length of stay was 5-7 days. The difference in length of stay among AKI and non- AKI cases was found to be highly significant (p=0.001)[Table 1].Mean serum bicarbonate levels among cases with AKI were less **(**15.96 ± 8.08 mmol/L) as compared to those without AKI (18.02 ± 5.36 mmol/L).The difference in serum bicarbonate levels was however not found to be statistically significant (p=0.092). Hyponatremia (<135 mEq/L) was more seen in AKI cases (32.4%) as compared to non-AKI cases (27.7%).

The difference in serum sodium status among AKI and non -AKI cases was found to be statistically significant (p=0.050).No statistically significant difference was observed in serum potassium and calcium status among AKI and non-AKI cases. Significant association was seen between duration of i.v. rehydration therapy and AKI (p=0.018)[Table 2].Renal replacement therapy was required in 14/37(37.8%) AKI cases.Among them,64.3% required peritoneal dialysis,28.6% required hemodialysis, while 7.1% required both peritoneal dialysis and hemodialysis.12.2% cases hospitalised for acute gastroenteritis expired in this study.

Mortality was more in AKI cases i.e. 27% as compared to non-AKI cases i.e. 6.4% and the difference was found to be statistically significant (p=0.003)[Table 1]. Out of 10 cases of AKI who expired,5 cases(i.e.50%) had AKI stage 3,while 3 cases(i.e.30%) had AKI stage 2 and 2 cases(i.e.20%) had AKI stage 1.However, no significant association was seen between AKI stage and outcome [Table 3].

Table 1 : Clinical Data Of Patients With Aki And Non-aki

	AKI (n=37), n(%)	Non-AKI (n=94), n(%)	Total n(%)	P -value
Age				0.914
6 months -2 years	15(40.5)	47(50)	62(47.3)	
2-5 years	7(18.9)	18(19.1)	25(19.1)	
5-10 years	7(18.9)	16(17)	23(17.6)	
10-15 years	8(21.6)	13(13.8)	21(16)	
Gender				0.201
Male	23(62.2)	45(47.9)	68(51.9)	
Female	14(37.8)	49(52.1)	63(48.1)	
Duration of symptoms before hospitalisation(days)				<0.001 (S)
1-3	10(27)	40(42.6)	50(38.1)	
3-5	7(18.9)	38(40.4)	45(34.3)	
5-7	5(3.5)	5(5.3)	10(7.6)	
>7	15(40.5)	11(11.7)	26(19.8)	
Clinical Presentation				
Loose motions	5(13.5)	14(14.9)	19(14.5)	0.941
Vomiting	5(13.5)	9(9.6)	14(10.7)	0.732
Loose motions + Vomiting	27(73)	71(75.5)	98(74.8)	0.936
Fever	32(86.5)	74(78.7)	106(80.9)	0.732
Cold extremities	32(86.5)	74(78.7)	46(35.1)	0.442
Impaired consciousness	20(54.1)	65(69.1)	81(61.8)	0.154
Pain abdomen	11(29.7)	16(17)	27(20.6)	0.168
Abdominal distension	0(0)	5(5.3)	5(3.8)	0.355
Dysentery	6(16.2)	8(8.5)	14(10.7)	0.322
Hydration status				0.056 (S)
No dehydration	11(29.7)	14(14.9)	25(19.1)	
Some dehydration	14(37.8)	30(31.9)	44(33.6)	
Severe dehydration	12(32.5)	50(53.2)	62(47.3)	
Length of stay(days)				0.001 (S)
<3	0(0)	2(2.1)	2(1.5)	
3-5	5(13.5)	27(28.7)	32(24.4)	
5-7	4(10.8)	32(34)	36(27.5)	
7-14	22(59.5)	28(29.9)	50(38.2)	
14-28	6(16.2)	5(5.3)	11(8.4)	
Urine output(ml/kg/hr) (Mean ± SD)	1.05 ± 0.93	1.20 ± 0.77		0.347
eGFR (Mean ± SD)	27.09 ± 26.50	53.01 ± 16.04		<0.001 (S)
Heart rate				0.646
Normal	30(81.1)	81(86.2)	111(84.7)	
Tachycardia	7(18.9)	13(13.8)	20(15.3)	
Duration of i.v. rehydration therapy(days)				0.018 (S)
≤3	8(21.6)	43(45.7)	51(38.9)	
4-7	18(48.7)	38(40.5)	56(42.7)	
>7	11(29.7)	11(13.8)	24(18.4)	
RRT				
Required	14(37.8)			
Not required	23(62.2)			
Type of RRT				
Peritoneal Dialysis only	9(64.3)			
Hemodialysis only	4(28.6)			
Peritoneal Dialysis + Hemodialysis	1(7.1)			
Outcome of cases				0.003 (S)
Improved	27(73)	88(93.6)	115(87.8)	
Expired	10(27)	6(6.4)	16(12.2)	

AKI-Acute kidney injury, RRT-Renal replacement therapy

Table 2 : Biochemical Data Of Patients With Aki And Non-aki

	AKI(n=37), n(%)	Non-AKI (n=94), n(%)	Total n(%)	p-value
Serum bicarbonate levels(mmol/L)	15.96 ± 8.08	18.02 ± 5.36		0.092

Serum sodium status (mEq/L)				0.050 (S)
Normal(135-145)	22(59.5)	42(44.6)	64(48.9)	
Hyponatremia (<135)	3(8.1)	26(27.7)	29(22.1)	
Hypernatremia (>145)	12(32.4)	26(27.7)	38(29)	
Serum potassium status(mEq/L)				0.936
Normal(3.5-5.5)	26(70.3)	63(67)	89(67.9)	
Hyperkalemia(>5.5)	4(10.8)	11(11.7)	15(11.5)	
Hypokalemia(<3.5)	7(18.9)	20(21.3)	27(20.6)	
Serum calcium status(mg/dl)				0.684
Normal (9-11)	14(37.8)	41(43.6)	55(42)	
Hypocalcemia(<9)	23(62.2)	53(56.4)	76(58)	

AKI-Acute kidney injury

Table 3: Outcome Of Cases In Relation To Aki Stage (kdigo)

OUTCOME	AKI STAGE					
	STAGE 1		STAGE 2		STAGE 3	
	No.	%	No.	%	No.	%
Improved	6	75	1	25	20	80
Expired	2	25	3	75	5	20
Total	8	100	4	100	25	100
Chi-square = 5.310 with 2 degrees of freedom; p = 0.070						

DISCUSSION

This is the first study on Indian pediatric population aiming to study proportion of children with AKI and associated risk factors in those hospitalized for acute gastroenteritis.AKI was diagnosed by taking into consideration both the creatinine and urine output criteria of KDIGO AKI staging[7].Compared to our prospective study, in a retrospective study by Marzuillo *et al*[11], only creatinine criteria of KDIGO staging was considered because urine output measurement was lacking. AKI was found in 24.6%patients hospitalized for acute gastroenteritis, which is slightly lesser than our study, maybe due to the fact that urine output criteria was not taken into consideration in that study leading to underdiagnosis of AKI cases. In a study conducted by Bradshaw *et al*[12] in the United States, it was described that 1% of patients with infectious diarrheal disease can develop AKI.In this study, however, the incidence of secondary diagnosis of AKI in children hospitalized with a primary diagnosis of diarrheal illness was evaluated searching the entire database on the basis of *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis without having access to clinical and biochemical data.Compared to study by Marzuillo *et al* [11]in which most cases had AKI stage 3,in our study, most cases had AKI stage 3 as our center being tertiary care center and having facility of dialysis, had referrals including critical cases as well from many states. Considering that the AKI detected by ICD-9-CM codes is likely to be the severe form, if we compare the prevalence found by Bradshaw *et al* [12], i.e. 1%, with proportion of children with stage 3 AKI (19.1%) in our study, the difference is quite huge. This huge difference, however, could still be explained by the different availability of access to medical care in developing countries40 with subsequent more later presentation to hospital as well as more dehydration in the latter patients.Imani *et al* [13] in their study showed that within the AKI group of patients with acute infections, 24 % were classified as stage 1, 35% as stage 2, and 41%as stage 3 AKI. In our study also, majority of cases had stage 3 AKI.

Majority of cases with AKI in our study were in the age group 6 months-2 years(40.5%).AKI was found more in males. Male : Female ratio was 1.64 : 1 Imani *et al*[13] in their study also showed that AKI was more common among infants (aOR = 1.6; 95 % CI, 1.1–2.1). In a study by Moghtaderi *et al*[14],the median age of the children with gastroenteritis was 2.5 years and 78.6% of them were males.The reason for this finding is not that gastroenteritis is more common in males, but maybe that the male patients are admitted early in the course of illness in this part of the country.

Bradshaw *et al*[12] identified CKD, hypertension and other kidney and genitourinary chronic conditions as risk factors for AKI in children with infectious diarrheal illnesses, but they did not examine other clinical and biochemical risk factors for AKI. So, we compared some of the potential risk factors between AKI and non-AKI group and statistically analysed them. In the present study, most of the cases with AKI (i.e. 40.5%) had duration of illness >7 days before hospitalisation while in most of the non AKI cases, duration of illness before hospitalization was 1-3 days (42.6%).The difference in duration of illness before hospitalization among AKI and non-AKI cases was found to be statistically significant (p<0.001). This indicates that longer duration of illness before hospitalisation was associated with AKI. This may be explained by the fact that longer duration indicates late presentation to hospital and so delay in intervention taken to correct the dehydration, leading to more chances of renal damage and so, AKI. Marzuillo *et al* [11] in their study also found that duration of symptoms before hospitalization was a significant and independent risk factor for AKI in children hospitalized for acute gastroenteritis(p<0.001).

Clinical presentations like presence of loose motions, vomiting, fever, pain abdomen, abdominal distension, dysentery and cold extremities were compared among AKI and non-AKI cases.Most common clinical presentation among cases with AKI was fever and cold extremities, i.e. 86.5%; however, the difference was not found to be statistically significant. However, in the study by Marzuillo *et al*[11],CRT > 2 sec and impaired consciousness(GCS<15) were found to be statistically significant risk factors of AKI with p-value of 0.06 and <0.001 respectively.Cold extremities and CRT > 2 sec indicate shock due to dehydration which can lead to AKI.

Out of 37 cases with AKI, 70.3% presented with dehydration (some dehydration or severe dehydration). Significant association was found between AKI and hydration status of cases (p=0.056).Similar to our study, Marzuillo *et al*[11]found that dehydration >5% and dehydration >10% were found statistically significant risk factors for AKI in children hospitalized for AGE(p-value <0.001). In study by Moghtaderi *et al*[14], out of the 140 children presenting with AKI after AGE,76(54%)children had severe dehydration and metabolic acidosis.

In our study,AKI was associated with longer length of stay. Similar findings were seen in studies conducted by Marzuillo *et al* [11], Basu *et al* [15], Alkandari *et al* [16], Kavaz *et al* ,Chang J-W *et al*, Volpon *et al* and Shalaby *et al* [17-20].

Mean serum bicarbonate levels among cases with AKI were less as compared to those without ,however, the difference not found to be statistically significant .Marzuillo *et al*[11] in their study also found that mean serum bicarbonate levels(mEq/L) were less in AKI patients as compared to non-AKI patients but in his study, lower bicarbonate levels were significantly associated with AKI patients as compared to non-AKI patients and so, low bicarbonate levels were considered risk factors of AKI. Imani *et al*[13] also, in their study showed that patients with AKI were more likely to present with a low serum bicarbonate,as compared to those without AKI. Hyponatremia was more seen in AKI cases as compared to non-AKI cases and this difference was found to be statistically significant,similar to the findings by Marzuillo *et al*[11].This may be due to fluid overload state seen in AKI and can be considered a significant risk factor of AKI. No statistically significant difference was observed in serum potassium and serum calcium status among AKI and non-AKI cases .

AKI was associated with more duration of i.v. rehydration as compared to non-AKI patients,similar to study by Marzuillo *et al*[11].Renal replacement therapy was required in 37.8% cases.Contrary to our study, in the studies by Marzuillo *et al* [11] and Moghtaderi *et al*[14] ,no cases with AKI required dialysis. Reason might be that being a tertiary care center, more cases presented in complicated states leading to more number of patients developing AKI and that too, severe and more patients requiring RRT. Also, sample size in our study was much higher than these studies. Mortality was more in AKI cases i.e. 27% as compared to non-AKI cases i.e. 6.4% and the difference was found to be statistically significant.However, no significant association was seen between AKI stage and outcome. Similar findings were there in study by Imani *et al*[13].

It can be concluded from our study that about one-third cases of AGE can develop AKI out of which one-third cases can develop AKI stage 3.Longer duration of illness before hospitalization, dehydration and hyponatremia are found to be significant risk factors of AKI in children hospitalized for AGE and so, particular attention should be paid to kidney health of patients with AGE, especially in the presence of increased duration of symptoms before hospitalization and dehydration. Early intervention by rehydration therapy can help prevent AKI in such patients. Also, AKI cases are associated with longer length of stay and more duration of i.v. rehydration therapy as compared to non-AKI cases and so, early seeking of medical advice will lead to less children landing up in AKI and so, lesser duration of stay in the hospital.

Limitations

Our study was conducted in a tertiary care center and many cases of gastroenteritis were treated in the periphery so, milder forms of AKI might be unrecognized leading to cases presenting to us in severe stages of AKI. Diet, as a major factor influencing creatinine was not considered in this study.Only short-term outcomes of cases were analyzed. Children with AKI may have long-term residual renal injury e.g. microalbuminuria, hypertension or elevated creatinine levels. Lack of information on the long-term outcomes does not permit evaluation of the impact of AKI on renal function in long run.

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Declaration of patient consent

Informed consent was obtained from all the patients.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

Ethical Approval

The study was reviewed and approved by the Institutional Ethics Committee of SMS Medical College & Hospital,Jaipur.

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