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ORIGINAL ARTICLE

Assessment of Kidney Status in Cardiac Children Treated With Angiotensin Converting Enzyme Inhibitors

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ABSTRACT

Background: Angiotensin Converting Enzyme Inhibitors (ACEIs) are commonly used to treat many cases especially chronic heart failure and there is different data about kidney affection in those patients, we aimed in this study to evaluate the kidney status in patients using this medication weather on chronic bases or recently added. **Patients and methods:** We studied 50 cardiac children 15 of them with old treatment with ACEIs group A, 15 of them with new treatment with ACEIs group B and 20 of them not use ACEIs as a control group as group C**,** all patients were subjected to detailed history taking including demographic data, Glomerular filtration rate calculated For children by modified Schwartz method in addition to Routine test of kidney function**.Results**: There was statistically significant higher creatinine level and lower eGFR in group A and B than control group, there was 40% of patients on old ACEIs treatment suffered from metabolic acidosis and increased creatinine level in blood compared to (10% and 20% among group B, 5% and 0% among group C respectively), while 50% of group A suffered of hyperkalemia and decreased GFR versus 20% among group B and 5% among group C respectively, and the difference between groups was statistically significant. There was a statistically significant negative correlation between duration using ACEIs and GFR and urine output .**Conclusion**: We concluded that there is high risk of renal impairment in cardiac children treated with ACEIs and this risk is higher with increasing duration of therapy with these drugs

Keyword: ACEIs; pediatric; heart failure; renal

INTRODUCTION

Angiotensin converting enzyme inhibitors (ACEI) are drugs widely used in pediatric cardiology. They are used to manage heart failure and hypertension [1,2]; as they are used to improve symptoms in children with congenital heart disease and left-to-right shunting or valve regurgitation [3]**.**

Despite ACEI being a mainstay of the medical management of pediatric cardiac disease, there is little or no evidence to guide how this drug should be introduced [4]**.** Children with heart disease more often commence ACEI as inpatients, pediatric formularies usually suggest starting with a low initial test dose (1 mg/kg captopril) and up titration, no guidance is founded to the safest or most effective method of reaching a target dose; because there are concerns that ACEI therapy in infants and very small children lead to hypotension and renal impairment [5].

Despite unambiguous recommendations to detect sudden renal impairment by monitoring serum creatinine before and after the start of ACEI treatment and to discontinue treatment if creatinine concentrations increase by 30% or more, recent data show that only 10% of patients receiving these drugs recommended monitoring and only 20% of those with a creatinine increase of 30% or more after starting ACEIs treatment discontinue the drugs [6], While Other Clinical trial data has indicated that ACEIs induced renal impairment is uncommon [7].

ACEIs role in acute kidney injury is not widely acknowledged because of the lack of relevant information and no study determined the incidence of acute kidney injury in children with chronic heart failure or congenital heart disease treated with Angiotensin converting enzyme inhibitors [5].

Aim of the work

To assess renal affection in children with chronic heart failure treated with ACEI weather chronically on it or ACEIs recently had been added.

PATIENTS AND METHODS

A case-control study was done in Cardio Unit of Pediatrics, Zagazig children University Hospitals, in the period from August 2018 till Feb 2019. We examined 50 children with chronic heart disease.Well-informed verbal and written consent were obtained from the parents or caregivers, and approval of health committee of IRB was obtained

We included Children from the ages of 1.5 year to 14 years with Chronic cardiac diseases heart failure and we excluded Patients outside the age group, Children with history of any renal disease or Children with acute cardic lesion

Patient group:

50 patients with chronic heart failure 15 of them in old treatment with ACEIs group A, 15 of them newly treated with ACEIs group B and 20 of them as a control group not treated with ACEIs group C.

- Group A: 15 patient in old treatment with ACEIs and recruited from pediatric cardiology outpatient clinic were 12 with congenital heart disease and 3 of them with rheumatic heart disease, the dose for all cases was 1m/kg/day and least duration was 12 month mean duration of usage was (1045 ± 130.7 day) ranging from 265 to 2190 day(1-6 years).
- Group B: 15 patient with new introduction of ACEIs; 12 of them with congenital heart disease and 3 of them with rheumatic heart disease, those patients were taken from inpatient of pediatric cardiology unit, The cause of admission in 12 patient was pneumonia with heart failure and 3 patient experienced Heart failure without predisposition, The dose for all cases was 1m/kg/day and least duration was 5 days.
- Group C: 20 patients as a control group with chronic heart failure not treated with ACEI, 14 of them were with congenital heart disease and 6 of them with rheumatic heart disease, and they were collected from outpatient clinic of pediatric cardiology unit

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

N.B. there was only 10% of patients on chronic use of ACEIs that complained of side effects in the form of dry cough vs no one of the other group on acute use of ACEIs.

Methods:

Data collected from all cases at the time of examination in outpatient clinic for both groups A and C and after 5 days of admission and introduction of ACEI in group B.

Collected variables were; Demographic information, admission diagnoses, comorbidities, height, weight, available laboratory values and vital signs were collected at the time of admission

Then Assessment of kidney had done by:

Routine test of kidney function: urine output, urea, creatinine, electrolyte (sodium, chloride, potassium, bicarbonate), uric acid, Arterial Blood Gases and estimated Ultrasound scan on abdomen and Glomerular filtration rate

Glomerular filtration rate: eGFR was calculated for children by Creatinine-Based Bedside Schwartz Equation (modified Schwartz method):-

Estimated Glomerular Filtration Rate =0.413 x (height/ standardized serum creatinine) if height is expressed in centimeters.
eGFR = mL/min/1.73 m2 Scr = mg/dL [8].

Data management and statistical analysis

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA), and Microsoft Office Excel 2010 for windows (Microsoft Cor., Redmond, WA, USA). Continuous Quantitative variables e.g. age were expressed as the mean ± SD & median (range), and categorical qualitative variables were expressed as a absolute frequencies "number" & relative frequencies (percentage). Continuous data were checked for normality by using Shapiro Walk test. Independent samples Student's t-test was used to compare two groups of normally distributed data while Mann-Whitney U test was used for non-normally distributed data. One way ANOVA test was used to compare more than two groups of normally distributed data while Kraskall Wallis H test was used for non-normally distributed data. Categorical data were compared using the Chi-square test or Fisher's exact test when appropriate. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following; P > 0.05: Non significant (NS) and P < 0.05: Significant (S)

RESULTS

Our results showed that the three studied groups were matched as regard age, no statistical significant difference among three studied groups as regard analysis of blood picture, HB, WBCs, RBCs and platelets count, there was no statistical significant difference among the three studied groups regarding laboratory tests, except creatinine level which was higher among group II (0.64 ± 0.35) and I (0.63 ± 0.36) treated with ACEIs compared to 0.39 0.21 among non-ACEIs group with a high statistical significant difference and there were a high statistical significant difference among the three studied groups regarding glomerular filtration rate and urine output which were higher among non-ACEIs group than the other two groups using ACEIs table **1**.

We found as well the main difference in glomerular filtration rate and urine output caused by group C, and both groups A and B were close to each other and the difference between them was statistically not significant table **2**.

As regard kidney assessment this study showed that 40% of patients on old ACEIs treatment suffered of metabolic acidosis and increased creatinine level in blood compared to (10% and 20% among group II, 5% and 0% among group III respectively), while 50% of group I suffered of hyperkalemia and decreased GFR versus 20% among group II and 5% among group III respectively, and the difference between groups was statistically significant table **3**.

Table **4** showed a statistically significant negative correlation between duration using ACEIs and GFR presented also in (figure**1**) ,and urine output, while there were no correlations between duration of ACEI and other tested parameters K level ,urea, creatinine, uric acid, Na and Mg.

We studied effect of used medication on eGFR table **5**, we found that the effect of ACEIs, Lasix and amikacin on eGFR was statistically significant among patients using these drugs, that they have lower glomerular filtration rate than those not using these drugs and after applying Multivariate Analysis on studied population who also used other medication as Lasix and Amikacin, of significant variables for eGFR affection; the use of Lasix and amikacin became non-significant predictors, while using ACEIs still statistically significant effector for eGFR table (**6**).

Table (1): demographic and laboratory data among the studied groups.

Variables	Group A (Old ACEIs) N=15	Group B (New ACEIs) N=15	Group C (Not used ACEIs) N=20	F test	P-value
Age/years				KW#	
Mean ±SD	39.7± 16.8	37 ± 17.8	50.1 ± 21.2	3.69	**0.158**
Range	16-72	18-72	18-92		
Hb					
Mean ±SD	10.5 ± 1.4	10.6 ± 0.88	10.3 ± 0.92	0.333	**0.72**
Range	8.4 – 14.6	9.6 – 12.6	8.8 – 12.1		
WBCs					
Mean ±SD	11.6 ± 3.6	13.3 ± 2.4	13.4 ± 2.6	1.9	**0.16**
Rang	3.9 - 17.8	10 - 16.8	9.5 - 17.8		
RBCs					
Mean ±SD	4.3 ± 0.59	4.5 ± 0.42	4.2 ± 0.52	0.525	**0.595**
Range	3.1 – 4.1	3.7 - 4.9	3.2 - 4.9		
Platelets					
Mean ±SD	312.5 ± 145.4	290.3 ± 87.3	305.7 ± 83.7	0.129	**0.879**
Range	128 - 634	170- 483	125 - 483		
Urea				KW#	
Mean ±SD	11.5 ± 6.1	10.2 ± 3.5	10.7 ± 2.2	0.438	**0.7**
Range	4.8 – 32	5.6 – 16.3	7.3 – 14.1		
Creatinin				KW#	
Mean ±SD	0.63 ± 0.36	0.64 ± 0.35	0.39 ± 0.21	15.9	**<0.001***
Rang	0.22 - 1.3	0.42 - 1.3	0.22 - 1.3		
Uric acid					
Mean ±SD	4.03 ± 0.75	3.8 ± 0.46	3.96 ± 0.42	0.65	**0.572**
Range	2.9 – 5.7	3.1 - 4.4	3.2 - 5.1		
Na					
Mean ±SD	138 ± 3.7	138.3 ± 4.3	137.7 ± 3.2	0.095	**0.91**
Range	131 – 144	132- 144	130 - 143		
K					
Mean ±SD	4.43 ± 0.9	4.3 ± 0.73	4.1 ± 0.4	1.3	**0.27**
Range	3.3 - 5.8	3.4 - 5.6	3.5 – 5.1		
Ca					
Mean ±SD	8.8 ± 0.91	8.99 ± 0.56	9.33 ± 0.34	3.38	**0.05**
Range	5.8 - 9.9	7.9 - 9.9	8.6 - 9.9		
Mg					
Mean ±SD	2.2 ± 0.48	2.5 ± 0.44	2.4 ± 0.24	2.1	**0.112**
Range	1.5 - 2.9	1.6 - 2.9	2.1 - 2.9		
Hco3					
Mean ±SD	21.7 ± 2.02	21.7 ± 1.7	21.5 ± 1.14	0.09	**0.914**
Range	17.9 - 27.1	18.3 - 23.9	19.9 - 23.9		
Co2					
Mean ±SD	34.9 ± 4.6	36.6 ± 4.9	34.8 ± 3.4	0.672	**0.515**
Range	28.2 - 44.1	30.2 – 43.1	27.1 - 40.4		
PH					
Mean ±SD	7.4 ± 0.06	7.4 ± 0.05	7.4 ± 0.04	0.459	**0.635**
Range	7.3 – 7.5	7.3 – 7.5	7.3 – 7.5		
eGFR					
Mean ±SD	79.9 ± 35.4	71.1 ± 25.3	124.2 ± 40.9	18.5	**<0.001****
Range	28.5 – 182	26 – 103	32 – 208.4		
Urine output					
Mean ±SD	332.5 ± 101.6	336 ± 123.9	404.5 ± 92.9	9.2	**0.01***
Rang	230 - 620	210 - 630	280 - 650		

***P-value<0.05 is siginificant** ****P-value<0.05 is significant** **#Krusskal-wallis test of non-parametric data**

Table (2): LSD within the studied groups in relation to glomerular filtration rate and urine output.

Variables	Mean difference Group A with	p	Mean difference Group B With	p
eGFR	Group B=8.77 Group C=-44.37	**0.533** **<0.001**	Group C=53.13	**<0.001**
Urine output	Group B=-3.55 Group C=-72	**0.93** **<0.05**	Group C=-68	**<0.05**

Table (3): Difference in renal affection among three studied groups

	Group A (Old ACEIs) N=15		Group B (New ACEIs) N=15		Group C (Not used ACEIs) N=20		X^2	P-value
	N	%	N	%	N	%		
Metabolic acidosis	4	40	1	10	1	5	**6.67**	**0.04**
Hyperkalemia	5	50	2	20	1	5	**8.43**	**0.01**
Decreased GFR	5	50	2	20	1	5	**8.43**	**0.01**
Increased creatinine	4	40	2	20	0	0.0	**8.65**	**0.01**

Table (4): Pearson`s correlation between duration of using ACEIs and renal impairment parameters.

	Duration of using ACEIs	
	r	P value
Urine output	**-0.767**	**<0.001****
eGFR	**-0.563**	**0.03***
K	-0.228	0.333
Urea	0.095	0.689
creatinin	0.044	0.854
Uric acid	0.247	0.293
Na	0.244	0.3
Mg	0.191	0.42
Hco3	-0.277	0.237

****P value<0.001 is high significant** ***P-value <0.05 is significant**

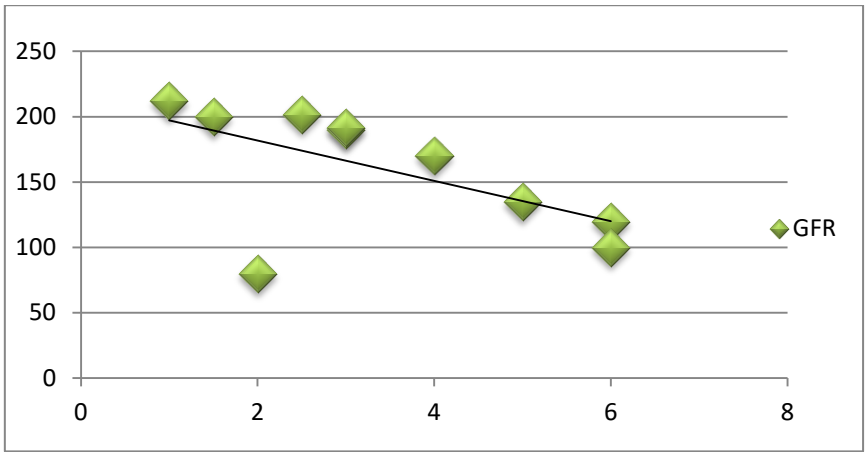

Figure (1): Negative correlation between duration using ACEIs and GFR

Table (5): eGFR of studied patients in relation to used drugs:

Variables	eGFR		MW-test	P-value
	Mean	±SD		
ACEIs **yes (N=30)** **no (N=20)**	76.9 124.2	±37.2 ± 40.8	3.86	**<0.001 (HS)**
Lasix **Yes (N=31)** **No (N=19)**	83.4 126.7	± 37.6 ± 35.6	2.56	**0.02 (S)**
Amikacin **Yes (N=35)** **No (N=15)**	78.1 118.9	± 37.04 ± 40.1	2.87	**0.01 (S)**
Claforan **Yes (N=33)** **No (N=17)**	94.4 118.9	± 42.7 ± 50.4	1.38	**0.19 (NS)**
Unasyn **Yes (N=34)** **No (N=16)**	101.02 99.3	47.9 40.2	0.113	**0.911 (NS)**

Table (6): Multivariate regression analysis to analyze significant predictors for eGFR among the studied group:

Variables	Regression coefficient		
		SE	P-Value
ACEIs	-0.349	0.099	**0.001**
Lasix	1.141	0.762	**0.128**
Amikin	-1.87	1.057	**0.109**
	r=0.896 , r^2 =0.803 **ANOVA P<0.000*** **Durbin-Waston ratio=1.768**		

DISCUSSION

ACEI are commonly prescribed drugs for hypertension, heart failure, diabetic microalbuminuria, and proteinuric renal disease and after myocardial infarction [9]**,** many post hoc analyses of clinical trials have examined the prognostic significance of deterioration in renal function after the start of ACEI treatment; in clinical trials of patients with heart failure, deterioration in renal function after starting ACEI treatment is commonly found [6].

Although level of creatinine increase after starting ACEIs treatment raises concern about the long term balance of risks and benefits, smaller increases (<30%) do not prompt consideration of treatment discontinuation according to current guidelines, The rationale for the 30% threshold in the context of adverse clinical outcomes is unclear**,** As little evidence is available on the actual risks associated with creatinine increases of less than 30% [7]**.**

Although this deterioration is associated with a poorer prognosis compared with patients with preserved renal function, the overall benefits of ACEIs treatment compared with placebo remain for cardiovascular outcomes and mortality [10]**.**

Considering the high prevalence of ACEIs use in general practice, any additional previously unrecognized risks would have major clinical and public health implications. we therefore conduct a case control study to assess kidney status in cardiac children treated with ACEIs; for this purpose we assessed kidney status in children with chronic cardiac diseases treated with ACEIs and not use ACEIs and set a comparison for detection the effect of ACEIs in kidney Status weather introduced for duration more than 12 m or recently added to treatment for 1st 5 days..

In our study, and regarding to new introduction of ACEIs there was a significant higher level of creatinine level than those without ACEIs treatment these results come in agreement with that of **Marsha et al** [10] that showed a common clinical problem arises when ACEIs are started and the serum creatinine became elevated above the patient's baseline level.

In our study, and regarding to old treatment of ACEIs there was a significant higher level of creatinine level and these results come in agreement with that of **Schmidt et al** [6] which stated that there are increased in the risk of decline in renal function, as measured by change in serum creatinine level, during prolonged ACEIs therapy .

Weather old or recent addition of ACEIs there was a kidney affection that was agreed with study of **Chikako Terano et al** [11,12] which state that increase incidence of kidney injury and its complications, such as hyperkalemia, decrease GFR in children with heart failure being treated with ACEIs

In this study there was significant higher incidence of metabolic acidosis, hyperkalemia, decrease GFR, and increased serum creatinine level in group AA on ACEIs chronically compared to group B with recently added ACEIs and group C without ACEIs.

The occurrence of metabolic acidosis was explained by **Irene and his colleagues** [13] who stated that ACE inhibitors lower aldosterone levels acting on angiotensin II, leading to insufficient re-uptake of sodium and excessive retention of H+, with resulting metabolic acidosis and these results come in agreement with our result as 40% of cases on old treatment of ACEIs and 10% of cases newly treated with ACEIs develop metabolic acidosis and this finding was confirmed by other researchers as **Elizabeth and her colleagues** [14]**.**

Ghassan et al (15) stated that Hyperkalemia within the first year of ACE-I therapy was relatively uncommon among people with estimated glomerular filtration rate >60 mL/min per 1.73 m^2 and there was a large increase in hyperkalemia risk among persons with low eGFR and these results come in agreement with our result as 20% of cases newly treated with ACEIs and 45% of cases on old treatment of ACEIs develop hyperkalemia.

The impact of using ACEIs was more on eGFR than Lasix and Amikacin; this was

in agreement with **Guadalupe et al** [16] as he found no significant difference of using amikacin in eGFR, also this came matched with **Paul et al** [17] who described that there was no significant effect of Lasix in eGFR on patients using ACEIs, while this was in contrary **et al** [18] who stated that the combination of ACEIs and diuretics affect eGFR more than those not using these drugs.

CONCLUSION

We concluded that there is high risk of renal impairment in cardiac children treated with ACEIs and this risk is higher with increasing duration of therapy with these drugs.

Declaration of interest :
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.
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