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Effect of Lisinopril on Microalbuminuria in Sickle Cell Anaemia Children: A Single-Blind Randomized Controlled Trial

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Abstract

Background

Sickle cell nephropathy is a major cause of morbidity and mortality in sickle cell anaemia (SCA). Proteinuria contributes to progression of renal damage. Icroalbuminuria is an early feature of SCN and progression to advanced kidney damage is delayed if regression is achieved with angiotensin converting enzyme inhibitors. We aimed to determine the effect of Lisinopril on microalbuminuria in children with SCA.

Materials and Methods

In this single-blind, two parallel-arm, placebo-controlled randomized trial study, 170 children aged 1-18 years with SCA and microalbuminuria were randomized into intervention and placebo groups using simple random sampling technique. The intervention and placebo groups received 0.1 mg/kg/day of Lisinopril and 100 mg/day of Vitamin C, respectively and were followed up for 3 months. Microalbuminuria and GFR were determined at baseline, 1, 2, and 3 months. Data were analyzed using SPSS software version 23.0.

Results

The mean baseline microalbuminuria was 134.2±72.5 mg/g in the intervention group and 107.6±58.0 mg/g in the placebo group (P= 0.009). The mean baseline GFR in the intervention and placebo groups were 122.0±35.6 ml/min/1.73m2 and 121.0±35.6 ml/min/1.73 m2, respectively. There was a significant regression of microalbuminuria in the intervention (84.6%), similar but higher than the placebo group (62.5%) at the end of 3 months' study. The mean GFR after 3 months on treatments was 115.4±26.3 ml/min/1.73 m2 and 117.0±33.9ml/min/1.73 m2 (p=0.055) in the intervention and placebo groups, respectively.

Conclusion

Lisinopril causes significant regression of initial microalbuminuria in children with SCA.

Key Words: Children, Sickle cell nephropathy, Microalbuminuria, glomerular filtration rate.

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1- INTRODUCTION

Worldwide, more than 300,000 babies with a sickle cell disorder are born each year (1). Haemoglobin disorders predominate in Africa with over 70% of all affected births occurring in this region and about 50% of these children living in Nigeria (1). Sickle cell anemia (SCA) accounts for more than three-quarters and is the most severe form of this disorder (2). Nigeria has the highest burden of SCA in the world with a prevalence of 20 per 1000 births (3). Sickle cell anemia affects virtually every organ of the body (4). Kidney involvement described as sickle cell nephropathy (SCN) is an important cause of morbidity and mortality in patients with SCA (5). Sickle cell nephropathy has prevalence that ranges from 5 to 18% (5, 6). Sickle cell nephropathy spectrum often begins with defects in urine concentration and acidification early in childhood and progresses with age to microalbuminuria, overt proteinuria, glomerulosclerosis, and renal failure (7).

Proteinuria is a frequent finding in SCA (5, 8). Although proteinuria is one of the earliest manifestations of SCN (7), it usually begins as hyperfiltration, microalbuminuria progressing to macroalbuminuria and overt proteinuria if kidney damage persists or no therapy is instituted (7). The prevalence of microalbuminuria in children with SCA ranges from 11.3 to 47.1% (9-11). Evidence has shown that the toxic effect of this protein accelerates the clinical course of renal impairment (12). However, this clinical progression can be halted or reversed by administration of angiotensin-converting enzyme inhibitors (ACEI) (13). The ACEI reduces hyper-perfusion, hyperfiltration, eliminates the toxic effect of proteinuria on renal tubules by reducing proteinuria, delays the development of intraglomerular hypertension and improves it where it has already developed (5, 14). The ACEIs do this by causing the constriction of the afferent arterioles and dilatation of the efferent arterioles thereby improving the hyper-perfusion and hyperfiltration injury that has been shown to underlay many of the pathogeneses of SCN (5). There has been comprehensive experience with the use of ACEIs in different clinical conditions in patients who do not have sickle cell anemia (14, 15). The few studies that reported reduction of microalbuminuria by ACEIs in patients with SCA were mainly conducted in adult population and outside Nigeria (13, 16, 17). Indeed, this effect in children requires evaluation, especially in Nigeria that has the highest burden of sickle cell anemia worldwide. The aim of this study was to determine whether ACEIs reduce microalbuminuria in children with SCA.

2- MATERIALS AND METHODS

2-1. Method

This was a single-blind randomized controlled trial, which was conducted in the sickle cell disease center at Federal Teaching Hospital, Gombe, (FTHG) North-east Nigeria, from September 2016 to March 2017. The FTHG is a 450-bed capacity tertiary institution with a sickle cell center where 50-70 children with SCA are reviewed weekly.

2-2. Inclusion and exclusion criteria

The study included children aged 1-18 years, with SCA and microalbuminuria who were in steady state (defined as the absence of fever, or crisis in the previous four weeks or more in a child who was not on any medication other than routine folic acid and prophylactic antimalarial drug) (18), who were being followed up in the sickle cell clinic at the Federal Teaching Hospital, Gombe (FTHG), and whose caregivers consented to the study. Children who were known to have hypertension, diabetes mellitus, HIV, and urinary tract infection were excluded from the study as these

conditions are secondary causes of microalbuminuria.

2-3. Ethical approval

All procedures performed were in accordance with the ethical standards of the institution research committee and with the 1964 Helsinki declaration and its later amendments. Written informed parental consent and assent were obtained in participants that were above 7 years of age, while ethical approval was obtained from the Research and Ethics Committee (REC) prior to the commencement of the study.

2-4. Recruitment and randomization

Interviewer-administered questionnaires were used to obtain detailed history and pertinent physical examination findings. Socio-economic index of each participant was determined using the method described by Oyedeji (19) in which parents' professions and educational attainment are used to categorize participants into any of five socioeconomic classes, class I being the highest and class V being the lowest socioeconomic class. The sample size was calculated using the formula for randomized controlled trial (20). Treatment effect was set at 0.8 in order to achieve 80% power of the two-tail score test set at $\alpha = 0.05$ (20).

The subjects with SCA and microalbuminuria who met the inclusion criteria were recruited consecutively on a weekly basis over four months. Participants who met the inclusion criteria were given well labeled universal bottles at clinic in the sickle cell center. Bigger containers were provided for female participants who could not void into the bottles directly. The samples were then transferred into the universal bottles by the participants. The older participants and parents were instructed on the method of midstream morning urine collection. On-the-spot preliminary dipstick urinalysis was carried out in the laboratory using Combi-screen strips (combi-11 multistrips) (URIC 10CF, GUILIN ZHONGUI CO. LTD 18B09) before microalbuminuria assay. Urine samples negative for proteinuria, hematuria, glucosuria, leucocytes were assayed for microalbuminuria and urinary creatinine while samples positive for these were excluded from the study, and such patients were sent for further evaluation for possible comorbidities. Participants who tested positive for microalbuminuria had their blood samples collected at the clinic for serum creatinine. The weekly recruitment and randomization were done in such a way that each participant had a 50:50 chance of being randomized into the intervention or placebo group (**Figures 1, 2**). Following randomization, subjects in each arm of the study received medication for three months. Oral Lisinopril at 0.1 mg/kg/day and oral vitamin C at 100 mg/day were administered to the intervention and placebo groups respectively. Medication adherence was monitored using indirect methods which included record taking, Morisky-8 Medication Adherence Scale, pill counts, and telecommunication systems (21, 22). The participants and their parents were blinded in this study.

2-5. Laboratory analysis

In all the participants who were recruited, microalbuminuria and serum creatinine were consecutively determined at baseline and monthly for 3 months after commencement of medications. Urinary albumin was determined by immunoturbidimetric method using Ichroma^{TM} MAU-25 and Ichroma^{TM} Reader (Boditech Med Inc., Gang-won-do Korea, PFR14K212338); while serum and urine creatinine were determined by modified Jaffe's reaction using Chemray 240 auto chemistry analyzer (Agape Diagnostics, Switzerland and GmbH) (23). Albumin-creatinine ratio (ACR) was calculated using the urine albumin concentration (mg/L) and urine creatinine (g/L). Albumin creatinine ratio of 30-300mg/g and ACR < 30mg/g

were classified as microalbuminuria and normoalbuminuria respectively (24), while GFR was derived from the serum creatinine using Schwartz formula (25).

2-6. Data analysis

Data were analyzed using SPSS version 23.0 (IBM, USA). Categorical variables (sex, age group, socio-economic status) were expressed in percentages and proportions while means and standard deviations were calculated for continuous variables (microalbuminuria GFR). Independent t-test (for differences in means between two independent groups), paired t-test (for differences in means in the same subjects), and Pearson correlation were used to determine the correlation between continuous variables while Chi-square test was computed to determine the level of statistical significance between categorical variables. P-value of <0.05 was considered to be statistically significant.

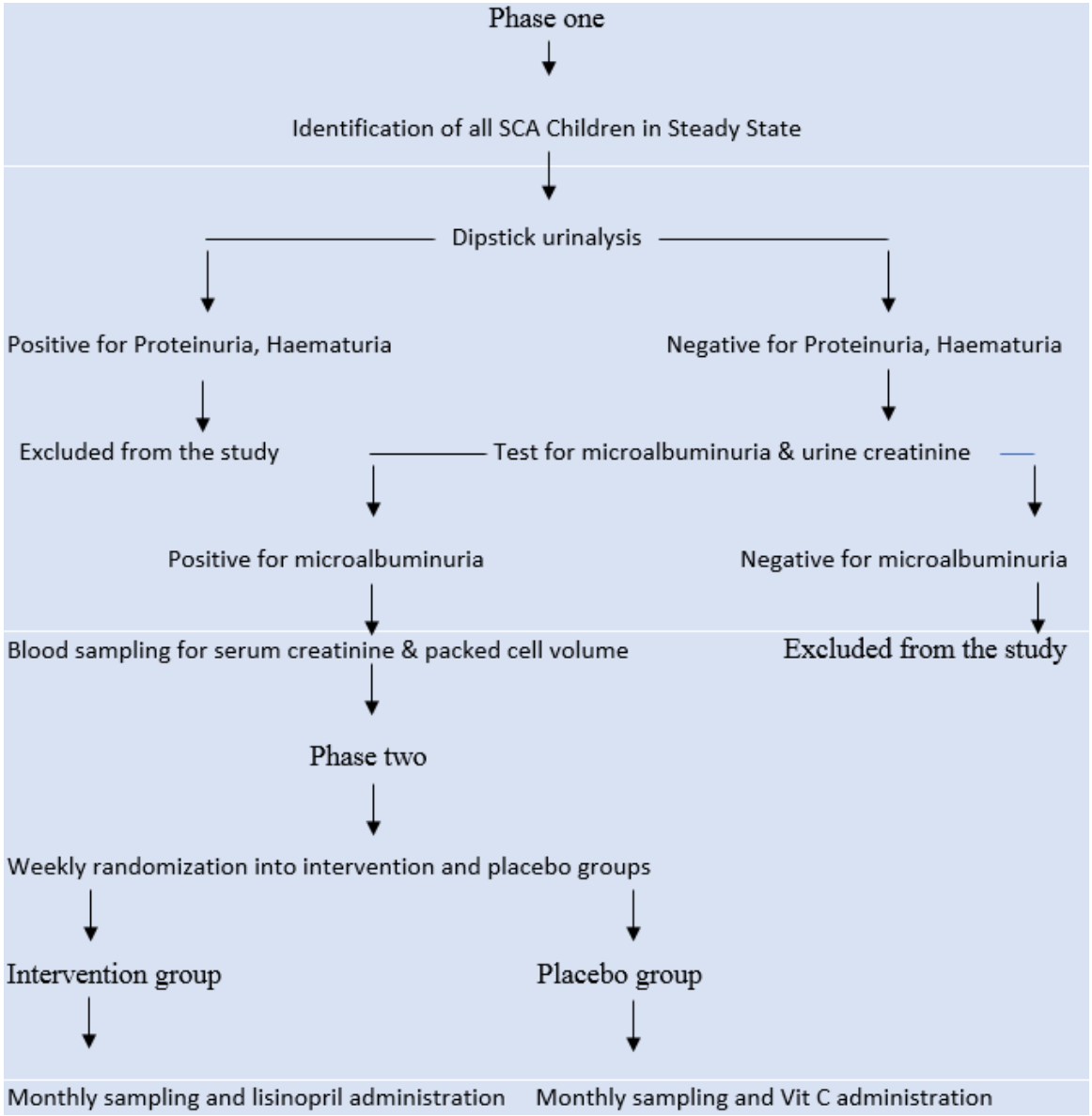

Fig.1: Summary of study protocol.

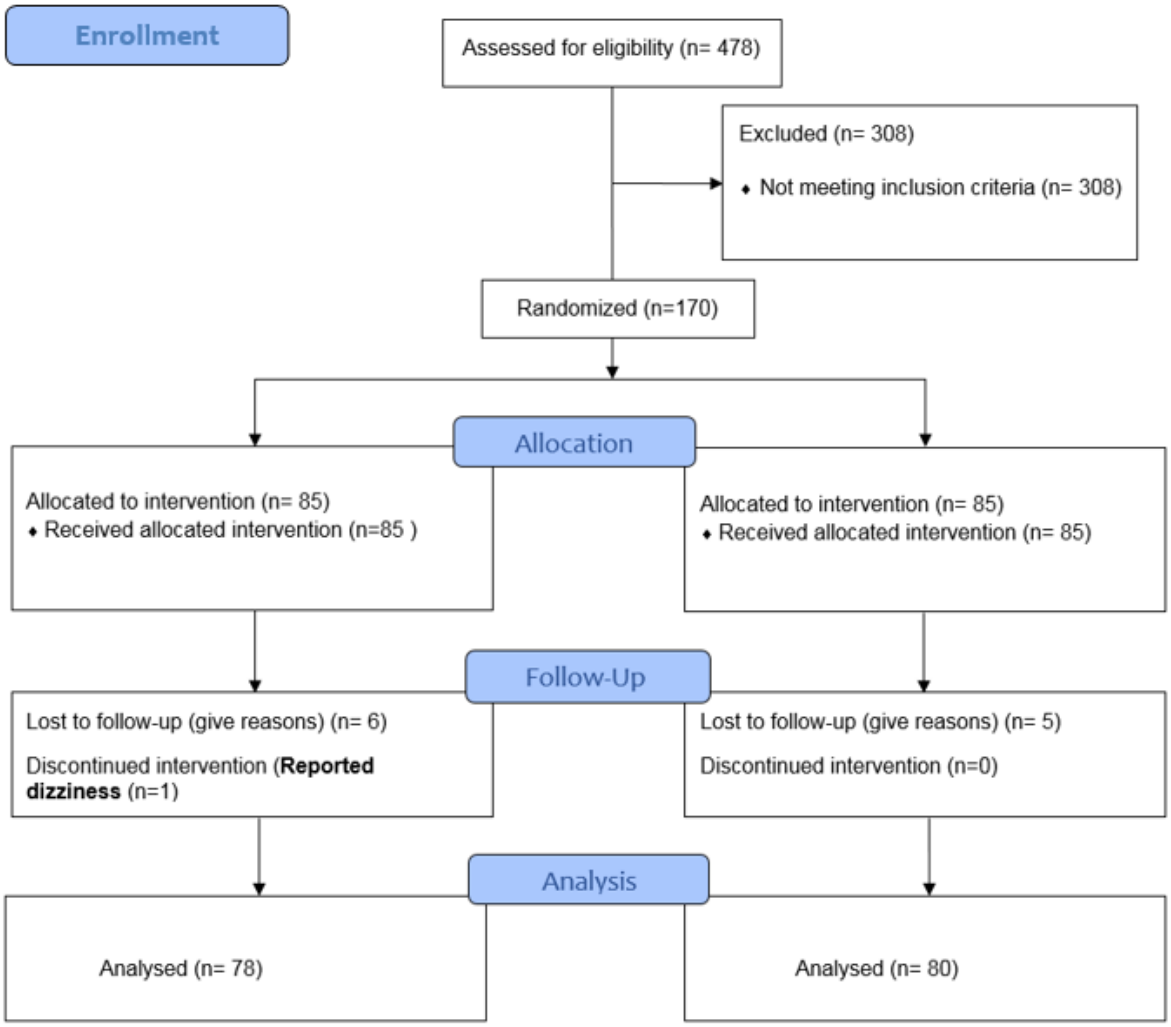

Fig.2: CONSORT 2010 Flow Diagram.

3- RESULTS

A total of 170 children with SCA and microalbuminuria were recruited into the study. Eleven children (six in the intervention group and five in the placebo group) were lost to follow- up while one child in the intervention was excluded from the study following the report of dizziness with intake of lisinopril. At baseline, data of 170 children with microalbuminuria were analyzed; while at 1, 2, and 3 months, the data of 158 remaining children were analyzed. The intervention group comprised 42 (49.4%) males and 43 (50.6%) females, M: F =1:1; while the placebo group comprised 45 (52.9%) males and 40 (47.1%) females, M: F= 1.1: 1, (p= 0.759). The mean ages of intervention and placebo group were 9.07±4.74 years and 7.64±4.88 years respectively, (p=0.054). The difference in proportions of male and females was not significant, (p=0.463) (**Table.1).** The mean ACR at baseline and after 3 months of medication administration was 134.2±72.5 mg/g and 6.5±1.1 mg/g in the intervention group, while the mean ACR at same periods was 107.6±58.0 mg/g and 7.9±1.1 mg/g in the placebo group. There was a significant reduction in the mean microalbuminuria in both groups at the end of the study although the reduction in the intervention group when compared to the placebo group was higher (p= 0.001) (**Table.2**). At the end of the study, microalbuminuria was found in a

significantly higher proportion of children in the placebo group when compared to those in the intervention group (37.5% vs. 15.4%, p = 0.001) **(Table.3 and Figure.3)**. The mean GFR at baseline and after 3 months of medication administration was 122.0±35.6 ml/min/1.73 m^2 and 115.4±26.3 ml/min/1.73m^2 (p= 0.001) in the intervention group, while the mean GFR was 121.0±35.6 ml/min/1.73 m^2 and 117.0±33.9 ml/min/1.73m^2 in the placebo group (p=0.094**) (Table.4)**.

Table-1: Socio-demographic characteristics of study subjects in both intervention and placebo groups (n=170).

Variables	Intervention (n = 85) Number (%)	Placebo (n = 85) Number (%)	P-value ǂ
Age group, years			
1 – 5	22 (25.8)	35 (41.1)	
6 – 10	33 (38.8)	22 (25.9)	0.463
11 – 15	15 (17.7)	23 (27.1)	
16 – 18	15 (17.7)	5 (5.9)	
Gender			
Male	42 (49.4)	45 (52.9)	0.759
Female	43 (50.6)	40 (47.1)	
Social class			
High	21 (24.7)	24 (28.2)	
Middle	23 (27.1)	21 (24.7)	0.859
Low	41 (48.2)	40 (47.1)	

ǂ Chi square P-value.

Table-2: Mean ACR and GFR of study subjects at baseline, 1, 2, and 3 months.

Variables	Intervention (Mean ± SD)	Placebo (Mean ± SD)	P-value ǂ
Microalbuminuria (mg/g)			
Baseline	134.2 ± 72.5	107.6 ± 58.0	0.009
1 month	7.6 ± 1.6	11.5 ± 2.9	<0.001
2 months	7.0 ± 1.4	8.0 ± 2.1	0.176
3 months	6.5 ± 1.1	7.9 ± 1.1	0.001
GFR (ml/min/1.73m^2)			
Baseline	122.0 ± 35.6	121.0 ± 35.6	0.789
1 month	117.8 ± 29.3	117.5 ± 30.2	0.822
2 months	121.0 ± 38.6	114.2 ± 32.6	0.829
3 months	115.4 ± 26.3	117.0 ± 33.9	0.055

SD: Standard deviation; GFR: Glomerular filtration rate; ACR: Albumin to Creatinine Ratio, ǂ Independent t-test P-value.

Table-3: Microalbuminuria categories at 1, 2 and 3 months.

Variables	Intervention (n = 78) Number (%)	Placebo (n = 80) Number (%)	P-value†
1 month			
Microalbuminuria	4 (5.1)	32 (40.0)	0.001
Normoalbuminuria	74 (94.9)	48 (60.0)	
2 months			
Microalbuminuria	12 (15.4)	19 (23.8)	0.248
Normoalbuminuria	66 (84.6)	61 (76.2)	
3 months			
Microalbuminuria	12 (15.4)	30 (37.5)	0.001
Normoalbuminuria	66 (84.6)	50 (62.5)	

†Chi square P- value.

Table-4: Comparison of mean GFR at baseline and at the end of the study in participants.

Study period	Intervention (Mean ± SD)	Placebo (Mean ± SD)
Baseline	122.0 ± 35.6	121.0 ± 35.6
3 months	115.4 ± 26.3	117.0 ± 33.0
P-value†	0.001	0.094

GFR: Glomerular filtration rate; SD: Standard deviation**;** †Paired t-test P-values.

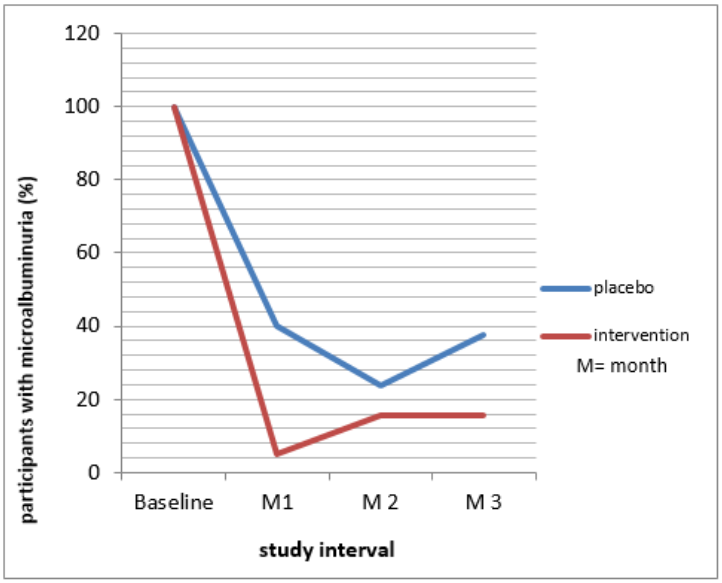

Fig.3: Trend of microalbuminuria over 3 month's study.

4- DISCUSSION

In this study, we aimed to determine whether ACEIs reduces microalbuminuria in children with SCA and compare this effect with the use of placebo, the proportions of intervention group with decrease in microalbuminuria at 1 and 3 months were higher than the placebo group. This is similar to findings by Foucan et al. (13), Aoki et al. (16), Falk et al. (17), Mckie et al. (26), and Fitzhugh et al. (27). At the end of this study, the percentage regression (subjects without microalbuminuria) was 84.6% in the intervention group. This is similar to Aoki et al.'s study (16) that reported regression in 75% of adults with SCA and macroalbuminuria. The slight difference in the regression rate might be because Aoki et al. studied adult populations and the fact that the participants had persistent macroalbuminuria was confirmed on 3 separate occasions, 15-30 days apart before the commencement of enalapril unlike in this study where lisinopril was commenced after one episode of microalbuminuria was demonstrated. Mckie et al. (26) reported a regression rate of 56% in children with SCA and macroalbuminuria. This lower regression rate might be because the participants in the study had macroalbuminuria, which is evidence of severe form of kidney damage compared with microalbuminuria in this current study. The persistent macroalbuminuria in the participants in the study by Mckie et al. (26) could also explain the lower regression rate. This is because persistent macroalbuminuria

suggests prolonged kidney impairment. Foucan et al. (13) reported lower regression rate of 37% and 17% in treatment and control group respectively. However, the study was conducted on adults who had persistent albuminuria, which probably explains the lower regression rates obtained. The regression of microalbuminuria seen in the placebo group in this study was to a lower degree than that demonstrated in the intervention group. This may be attributed to spontaneous regression. Mckie et al. and Perkin et al. (26, 28) have reported similar spontaneous regression. Whereas Perkin et al. (28) reported spontaneous regression in 40-60% of patients with initial microalbuminuria; Mckie et al. (26) demonstrated spontaneous regression of albuminuria in 62.1% of children with initial albuminuria during the recruitment phase (28). Children with initial microalbuminuria rather than persistent microalbuminuria were the subjects in the current study. Foucan et al. (13) reported progression of microalbuminuria in the placebo group. This may be because adults with SCA who might have prolonged damage to the kidney were the subjects in the study. This explains the reason the subjects in Foucan et al.'s study had persistent microalbuminuria,which is evidence of prolonged and severe damage to the kidney unlike in the Mckie et al. study (28), and this study. Another possible explanation for the regression of microalbuminuria seen in the placebo group in the current study may be attributed to the antioxidant effect of Vitamin C used as placebo in this study. Oxidative stress and increased inflammatory markers have been shown to contribute to the renal damage in SCA (29). Thus, the Vitamin C would have mopped up the inflammatory markers in the placebo group contributing to the regression demonstrated. At the end of this study, the mean glomerular filtration rate (GFR) of the intervention and the placebo group were less than the baseline GFR, though still within the normal range.

The mean GFR change observed in the intervention group was higher than the placebo group. This is however not surprising as hyperfiltration has been postulated as one of the mechanisms of microalbuminuria (30). Increased GFR (hyperfiltration) is one of the early manifestations of kidney damage in children with SCA, it causes hyperfiltration injury to the kidney and over time leads to microalbuminuria, both causing progression to advanced kidney damage (12, 30). The implication of this is that normal GFR in SCA patients with microalbuminuria may indicate already progressing kidney damage. Early administration of Lisinopril, which will cause reduction of high GFR (hyperfiltration) that would have led to further hyperfiltration injury, will thus be useful in children with SCA, microalbuminuria, and hyperfiltration.

4-1. Study Limitations

The use of vitamin C as a placebo in this study was a limitation. It would have been more appropriate to use a placebo indistinguishable from Lisinopril and that has no renal protective effect.

5- CONCLUSION

Lisinopril causes significant complete regression of initial microalbuminuria in children with SCA. More studies on the effects of Vitamin C in children with SCA and persistent microalbuminuria are highly recommended.

6- ACKNOWLEDGEMENTS

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7- CONFLICT OF INTEREST: None.

8- REFERENCES

1. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ. 2008; 86(6): 480-7.

2. Adekile AD, Olanrewaju A. Haemoglobinopathies. In: Azubuike JC, Nkanginieme KE. Paediatrics and child health in a tropical region. 2nd ed. Owerri, Nigeria: African Educational Services. 2007: 373-90.

3. World Health Organisation. Sickle cell anaemia. Report by secretariat. Available at: http://www.who.int./gb/archive/pdf_files/WHA59_9_en.pdf.Accessed December 07, 2015. 2015.

4. Powars DR. Sickle cell anemia and major organ failure. Hemoglobin. 1990; 14(6): 573-98.

5. Nath KA, Hebbel RP. Sickle cell disease: Renal manifestation and mechanisms. Nat Rev Nephrol. 2015; 11 (3): 161.

6. Stallworth JR, Tripathi A, Jerrell JM. Prevalence, treatment, and outcomes of renal conditions in pediatric sickle cell disease. South Med J. 2011; 104(11): 752-6.

7. Guasch A, Cua M, Mitch WE. Early detection and the course of glomerular injury in patients with sickle cell anemia. Kidney Int. 1996; 49(3): 786-91.

8. Anigilaje EA, Adedoyin OT. Persistent proteinuria among sickle cell anaemia children in steady state in Ilorin, Nigeria. Int J Med Sci. 2016; 8(3): 30-5.

9. Solarin AU, Njokanma FO, Kehinde O. Prevalence and clinical correlates of microalbuminuria among children with sickle cell anaemia. Afr J Paed Nephrol 2014; 1: 37-45.

10. Thompson J, Reid M, Hambleton I, Serjeant GR. Albuminuria and renal function in homozygous sickle cell disease: observations from a cohort study. Arch Intern Med. 2007; 167(7): 701-8.

11. Yaguo L. Microalbuminuria in children with sickle cell anaemia. Por Med J. 2011; 5: 157-64.

12. Abbate M, Zoja C, Remuzzi G. How does proteinuria cause progressive renal damage? J Am Soc Nephrol. 2006; 17(11): 2974-84.

13. Foucan L, Bourhis V, Bangou J, Mérault L, Etienne-Julan M, Salmi RL. A randomized trial of captopril for microalbuminuria in normotensive adults with sickle cell anemia. Am J Med. 1998; 104(4): 339-42.

14. Ahmad J, Siddiqui MA, Ahmad H. Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. Diabetes care. 1997; 20(10): 1576-81.

15. Hallab M, Gallois Y, Chatellier G, Rohmer V, Fressinaud P, Marre M. Comparison of reduction in microalbuminuria by enalapril and hydrochlorothiazide in normotensive patients with insulin dependent diabetes. Br Med J. 1993; 306(6871): 175-82.

16. Aoki RY, Saad ST. Enalapril reduces the albuminuria of patients with sickle cell disease. Am J Med. 1995; 98(5): 432-5.

17. Falk RJ, Scheinman J, Phillips G, Orringer E, Johnson A, Jennette JC. Prevalence and pathologic features of sickle cell nephropathy and response to inhibition of angiotensin-converting enzyme. N Engl J Med. 1992; 326(14): 910-5.

18. Olanrewaju DM AA. Anthropometric status of sickle cell anaemia patients in Ile-Ife. Niger Med Pract 1989; 18: 63-6.

19. Oyedeji G. Socio-economic and cultural background of hospitalized children in Ilesa. Niger J Paediatr. 1985;12:111-7.

20. Tango T. Sample size formula for randomized controlled trials. Statistics & Probability Letters. 2009;79(4):466-72.

21. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005; 353(5): 487-97.

22. Shalansky SJ, Levy AR, Ignaszewski AP. Self-reported Morisky score for identifying nonadherence with cardiovascular medications. Ann Pharmacother. 2004; 38(9): 1363-8.

23. Chesbrough M. District Laboratory Practice in Tropical Countries (Part 1).

Cambridge University Press, Cambridge, UK; 2002.

24. Hogg RJ, Portman RJ, Milliner D. Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification: National Kidney Foundation; 2002.

25. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatric clinics of North America. 1987; 34(3): 571-90.

26. McKie KT, Hanevold CD, Hernandez C, Waller JL, Ortiz L, McKie KM. Prevalence, prevention, and treatment of microalbuminuria and proteinuria in children with sickle cell disease. J paediatr hematol oncol. 2007; 29(3): 140-4.

27. Fitzhugh CD, Wigfall DR, Ware RE. Enalapril and hydroxyurea therapy for children with sickle nephropathy. Paediatr Blood cancer. 2005; 45(7): 982-5.

28. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. N Engl J Med. 2003; 348(23): 2285-93.

29. Uadia P, Gadzama A. Correlation of oxidative stress and inflammatory markers with the severity of sickle cell nephropathy. Ann Afr Med. 2010; 9(3):141-6.

30. Aygun B, Mortier NA, Smeltzer MP, Hankins JS, Ware RE. Glomerular hyperfiltration and albuminuria in children with sickle cell anaemia. Paediatr Nephrol 2011; 26: 1285-90.