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Effect of camel milk administration on oxidative stress in sickle cell anemic patients

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ABSTRACT

Objective: Sickle cell anemia (SCA) is one of the leading causes of child morbidity and mortality in Nigeria. About 25% of the country's population is carriers of the mutant gene responsible for the disease. Free radicals promote irreversible sickling of red blood cells and damage its membrane. This study was designed to evaluate the effect of camel milk administration on oxidative stress biomarkers in SCA patients.

Methods: Forty-five children aged 5–15 years old were recruited for the study. The patients were randomly divided into three groups, 1) HbAA: control group administered with 10 ml/kg of camel milk, 2) HbSS-1: SCA subject administered with routine SCA drugs, 3) HbSS-2: SCA administered with SCA drugs plus 10 ml/kg of camel milk.

Results: It was observed that 3 weeks of camel milk administration had resulted in significant changes in oxidative stress biomarkers. Serum level of glutathione, vitamin C and E were significantly increased ($P < 0.05$) in HbAA and HbSS-2 subject compared to HbSS-1. Similarly, the activities of antioxidant enzymes (superoxide dismutase activity and catalase) were increased due to the camel milk administration. On the other hand, serum malondiayldehyde (MDA) level decreases in all the groups investigated (HbAA, HbSS-1, and HbSS-2). MDA level significantly decreased in HbSS-2 at the third week of camel milk administration compared to other groups.

Conclusion: These findings suggest that camel milk could be beneficial in decreasing oxidative stress by improving the activities of antioxidant enzymes, and increasing the level of non enzymatic antioxidants in SCA patients. Thus, camel milk could be used in relieving the conditions of SCA patients.

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KEYWORDS

Camel milk; sickle cell anemia; antioxidants; oxidative stress

Introduction

Sickle cell anemia (SCA) is a gene-based disorder characterized by abnormal shape (sickling) of red blood cells (RBCs) when they become deoxygenated. This condition affects millions of people globally and is most prevalent among sub-Saharan Africans and the Western Hemisphere [1]. It was previously reported that 25% of Nigerian adults have sickle cell trait and 1%–3% are suffering from SCA [2]. About 150,000 babies born with the disease every year and not more than 5% of the children surviving to the age of 10 years [3].

The primary cause of the clinical symptomatology of SCA, which leads to the debilitating microvascular occlusions, hemolytic anemia, and chronic inflammation, is the intracellular polymerization of sickle hemoglobin (HbSS) that occurs when sickle erythrocytes are partially deoxygenated under the hypoxic conditions [4,5]. The clinical manifestations of the disease are quite variable and complications affect various organs and systems, including skeletal, genitourinary, gastrointestinal, spleen, liver, heart, and central nervous systems [6]. In SCA, the red cells have a shortened lifespan of 16–20 days—in contrast to a lifespan of 120 days in normal red cells. Vaso-occlusion is caused by the blockage of small vessels, by sickle-shaped RBCs, resulting in tissue infarction and painful crisis; this forms the most

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common clinical features of SCA. Large blood vessels are damaged, resulting in complications such as pulmonary hypertension and stroke which causes repeated endothelial damage to adherent sickle cells, complicated by vasoconstriction and deficit of endogenous vasodilator (NO) [7].

Nutritional approach in the management of sickle cell disease has been considered as an effective protocol adopted to relief the complications of the disease. Scientific investigations proved that deficiencies or low levels of various antioxidants, some of which are exacerbated the sickling episode or/and its complications [8,9].

In many Nigerian communities especially the northern part of the country, the use of camel milk is becoming more interesting; due to the folklore stories and scientific reports supporting its therapeutic potentials against a wide range of diseases such as anti-carcinogenic, anti-hypertensive [10,11], hepatoprotective effect, and antidiabetic effect [12], as well as antimicrobial activity [13]. Most a times, the therapeutic benefit of camel milk was link to its nutritional composition and its antioxidant potentials. The present study was designed to investigate the potentials of camel milk against oxidative stress in sickle cell anemic patients.

Materials and Methods

The subjects for this study were sickle cell anemic patients aged 5–15 years attending sickle cell clinic at Specialist Hospital Sokoto, Nigeria.

Collection of camel milk

Fresh camel milk was obtained daily by hand milking with the help of camel's herd residence of Yabo Local Government area, Sokoto state. The milk was dispensed directly in a sterile screw bottles kept in an icebox till required for use.

Experimental design

Forty-five patients of both genders aged 5–15 years attending the SCA clinic at Specialist Hospital Sokoto were recruited and grouped into three as follows:

Group 1

Normal: Control (HbAA) group administered with 10 ml/kg/day of fresh camel milk.

Group 2

Sickle cell anemic (HbSS-1) patients administered with 5 mg/day folic acid and 100 mg/kg paludrine (routine sickle cell anemia drugs) only.

Group 3

Sickle cell anemic (HbSS-2) patients administered with 5 mg/kg of folic acid and 100 mg/day paludrine (routine sickle cell anemia drug) and 10 ml/kg/day of fresh camel milk.

Sample collection

After obtaining written consent from all the parents/guardians of the subjects, 3 ml of blood sample were collected from each subject. The blood samples were centrifuged and the serum was used for antioxidants analyses.

Analyses of antioxidants

Glutathione

Determination of reduced glutathione (GSH) was achieved by the method of Patterson and Lazarow [14]. GSH reacts with an excess of alloxan to produce a substance with an absorption maximum at 305 nm.

Superoxide dismutase activity

Superoxide dismutase activity (SOD) was measured by the method of Zou et al. [15]. This method utilizes the inhibitory effect of SOD enzyme on auto-oxidation of pyrogallol.

Catalase

Assessment of catalase activity was done by the method of Beers and Sizer [16]. The assessment is base on the disappearance of peroxide which was followed spectrophotometrically at 240 nm. One unit decomposes one mole of H_2O_2 at 25°C and pH 7.0 under specified condition.

Malonyldialdehyde

Serum malonyldialdehyde (MDA) level as index for lipid per oxidation was evaluated by the method of Hartman [17]. The assay is based on the reaction of MDA with thiobarbituric acid, forming an MDA-TBA_2 adduct that absorbs strongly at 532 nm. The protein in serum was precipitated by trichloroacetic acid and then removed by centrifugation.

Vitamin C

Method by Rutkowski et al. [18] was adopted for the determination of vitamin C. The assay is based the reaction of ascorbic acid and copper II ion. The ascorbic acid is oxidized to form dehydroascobic acid, which react with 2,4-dinitrophenylhydrazine to form a red osazone that is measured spectrophotometrically at 250 nm.

Vitamin E

Serum vitamin E level was assessed by the method by Rutkowski et al. [19]. Vitamin E reduces ferric ion to ferrous ion which then form a red colored complex with α, α-1-dipyridyl and measured at 539 nm.

Data analysis

All data were computed as mean ± standard error of the mean and presented in figures. Result was analyzed statistically using statistical package for Social Science (SPSS) version 20. One-way analysis of variance was used to establish the differences between the means. Values were considered statistically significant at $P < 0.05$.

Results

Result of serum GSH level was presented in Figure 1. It was revealed that HbAA and HbSS-2 were significantly increased at the second week and third compared to HbSS-1. No significant difference as observed in the comparison made between HbAA and HbSS-2 throughout the experimental period.

Figure 1.

Result of serum SOD activity was presented in Figure 2. It was observed that HbSS-1 and HbSS-2 remain statistically similar ($P > 0.05$) at zeroth, first, and second weeks and differ significantly ($P < 0.05$) at third week. There was also progressive increase in SOD activity of HbAA from first to third weeks, and the increase as significant ($P < 0.05$) at second and third weeks compared to HbSS-1. On the other hand, SOD activity of HbSS-2 remain similar ($P > 0.05$) in the first and second weeks and rapidly increased significantly at the third week compared to HbSS-1 and remain similar ($P > 0.05$) to that of HbAA.

Figure 2.

The result of effect of camel milk administration on catalase activity was presented in Figure 3. It was noted that catalase activity showed o significant changes in HbSS-1 throughout the experimental period. While in HbAA and HbSS-2, the activity of catalase increased progressively from first to third weeks. The increase was significant ($P < 0.05$) at the third week compared to HbSS-1. No significant difference ($P > 0.05$) was observed in the comparison made between the three groups at first and second weeks.

Figure 3.

Serum vitamin C level was presented in Figure 4. The result shows that no significance increase was observed in both HbAA and HbSS-1 from first to second weeks. However, vitamin C level in HbAA was

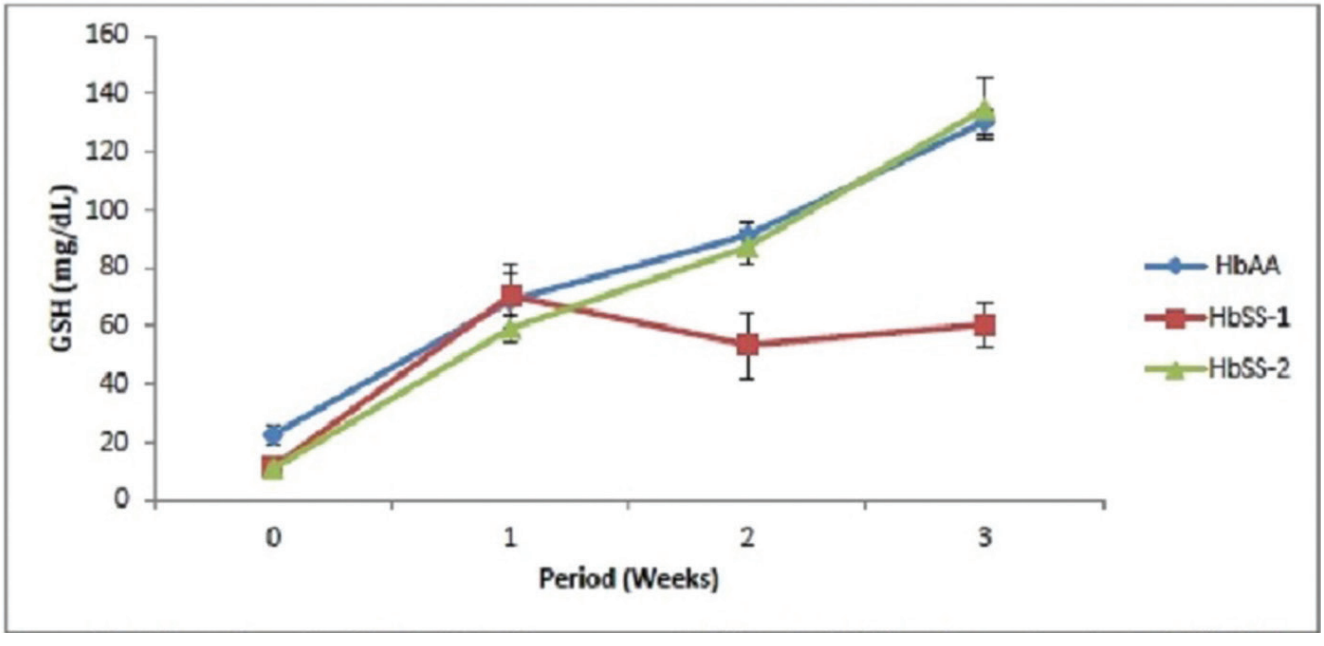

Figure 1.0: Effect of camel milk administration on serum GSH level of sickle cell anemia patients. GSH: Reduced glutathione. Normal; HbAA: Control group, administered with 10ml/kg/day of fresh camel milk. HbSS-1: Sickle Cell Anaemic patients administered with 5mg/kg of folic acid and 100 mg/day of paludrine. HbSS-2: Sickle Cell Anaemic patients administered with 5 mg/kg of folic acid and 100 mg/day of paludrine and 10 mL/kg/day of fresh camel milk.

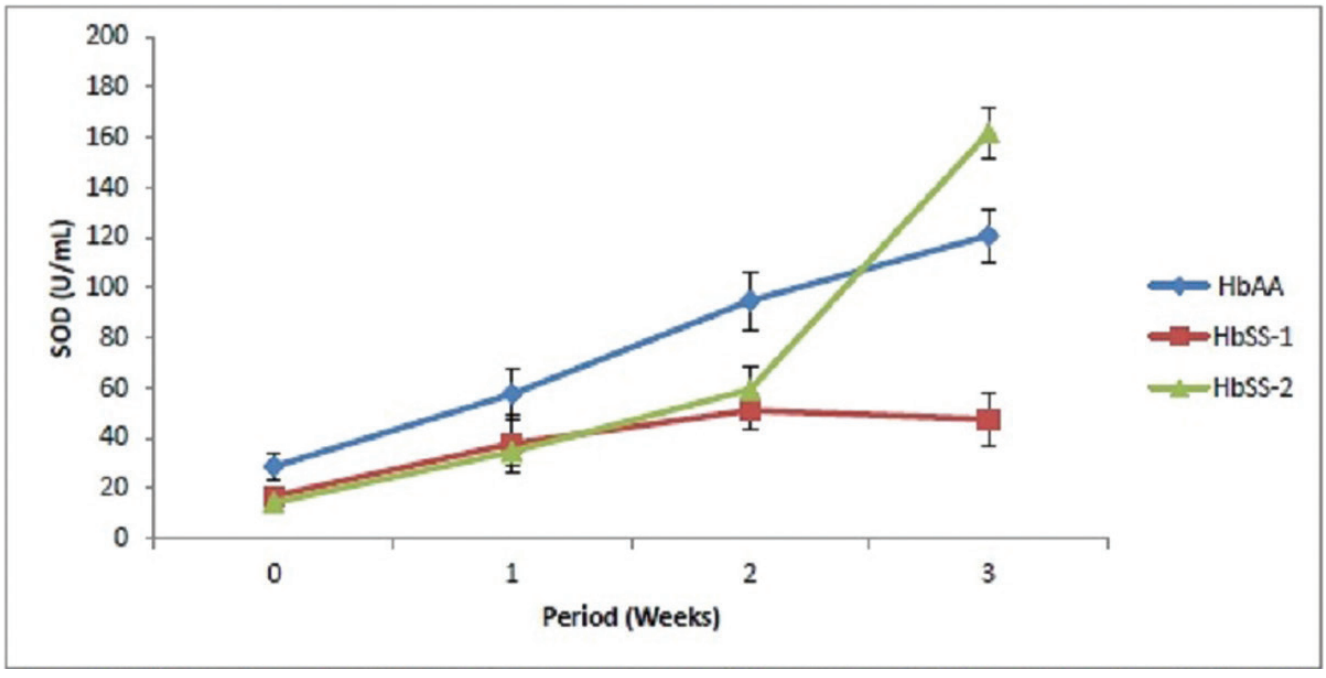

Figure 2.0: Effect of camel milk administration on serum SOD activity of sickle cell anemia patients. SOD: Superoxide dismutase. Normal; HbAA: Control group, administered with 10 ml/kg/day of fresh camel milk. HbSS-1: Sickle Cell Anaemic patients administered with 5 mg/day of folic acid and 100 mg/day of paludrine. HbSS-2: Sickle Cell Anaemic patients administered with 5 mg/kg of folic acid and 100 mg/day paludrine and 10 mL/kg/day of fresh camel milk.

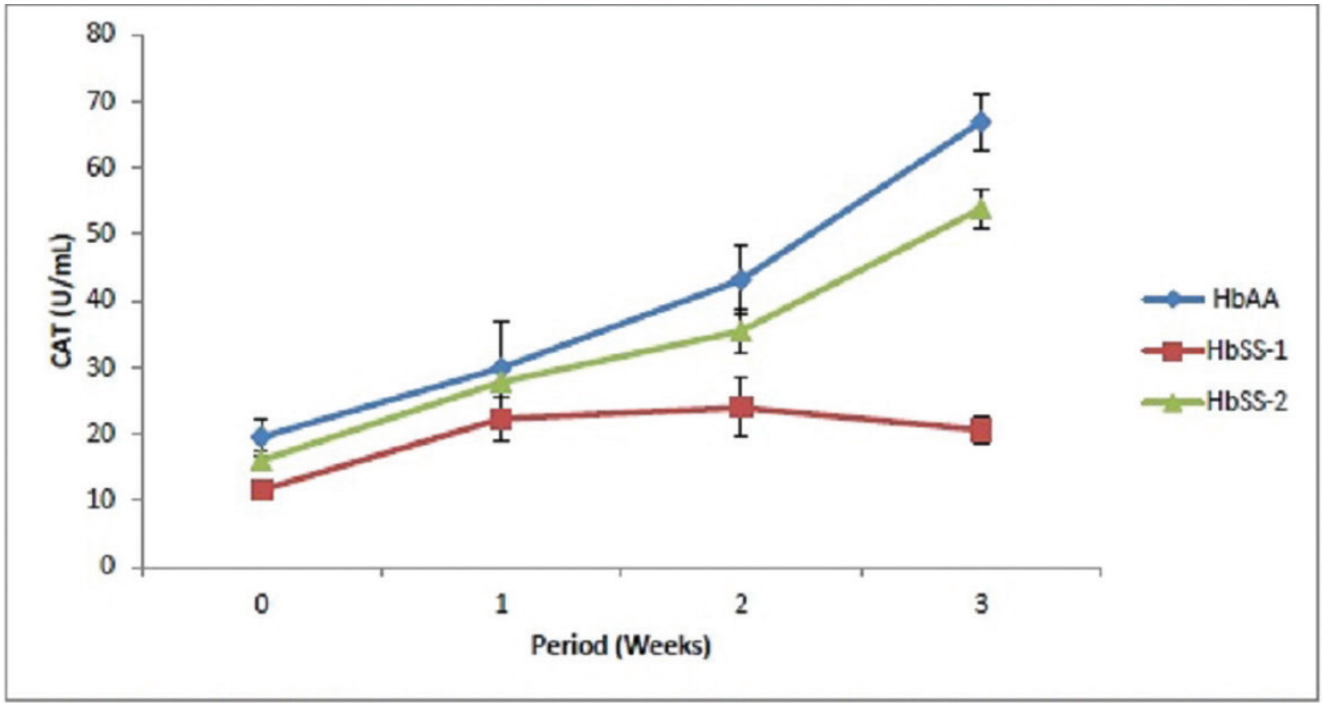

Figure 3.0: Effect of camel milk administration on serum catalase activity level of sickle cell anemia patients CAT: Catalase. Reduced glutathione. Normal; HbAA: Control group, administered with 10 ml/kg/day of fresh camel milk. HbSS-1: Sickle Cell Anaemic patients administered with 5 mg/day of folic acid and 100 mg/day of paludrine. Hbss-2: Sickle Cell Anaemic patients administered with 5 mg/kg of folic acid and 100 mg/day of folic acid and 100 mg/day of paludrine and 10 mL/kg/day of fresh camel milk.

later increased significantly ($P < 0.05$) at the third week compared to HbSS-1, whereas serum vitamin C in increased progressively in HbSS-2 throughout the experimental period and differ significantly

to HbSS-1 at second and third weeks. It was also observed that serum vitamin C in HbSS-2 was significantly increased ($P < 0.05$) compared to HbAA at the second week.

Figure 4.

The result of serum vitamin E level was presented in Figure 5. It was found out that vitamin E levels in HbAA and HbSS-2 were progressively increased as the period of administration increased and both appeared significantly different ($P < 0.05$) to that of HbSS-1 at the third week. HbSS-1 smoothly increased from first to second week and later declined at the third week.

Figure 5.

The result of MDA level as marker for oxidative stress was presented in Figure 6. It was observed that all the three groups (HbAA, HbSS-1, and HbSS-2) were progressively decreased with increasing period of drug and milk administration. No significant difference was observed in the comparison made between the groups from first to second week. On the other hand, the serum MDA level of HbSS-2 decreased significantly ($P < 0.05$) at third week compared to HbSS-1.

Figure 6.

Discussion

SCA is a hereditary disorder associated with oxidative cellular injury due to oxidants and antioxidants imbalance in erythrocytes that usually results in hemolysis [20]. It was long established that HbSS patients produce greater quantities of O_2^-, H_2O_2, and OH^- than HbAA subjects with normal RBCs [21].

This study revealed that 3 weeks of camel milk administration resulted in significant increase in GSH concentration of HbAA and HbSS-2. This increase was observed after the first week of camel milk administration which could be attributed to the antioxidant nutrients constituents of the milk. Camel milk is rich in vitamins A, B_2, C, and E [22]. Vitamin E has been known to enhance GSH production [23,24]. In addition, the fact that vitamins E and C are strong antioxidant molecules, their presence in circulation may spare the use of other antioxidant molecules including GSH, this could result to increased serum level of GSH. The present result is in agreement with the previous studies that reported decreased GSH concentrations in erythrocytes of SCA patients [20,25]. Contrary to this, Kiessling et al. [26] reported that GSH synthesis is not diminished in SCA patients. A study by Reid et al. [27] reported 57% increase in GSH synthesis in SCA patients compared to normal subjects,

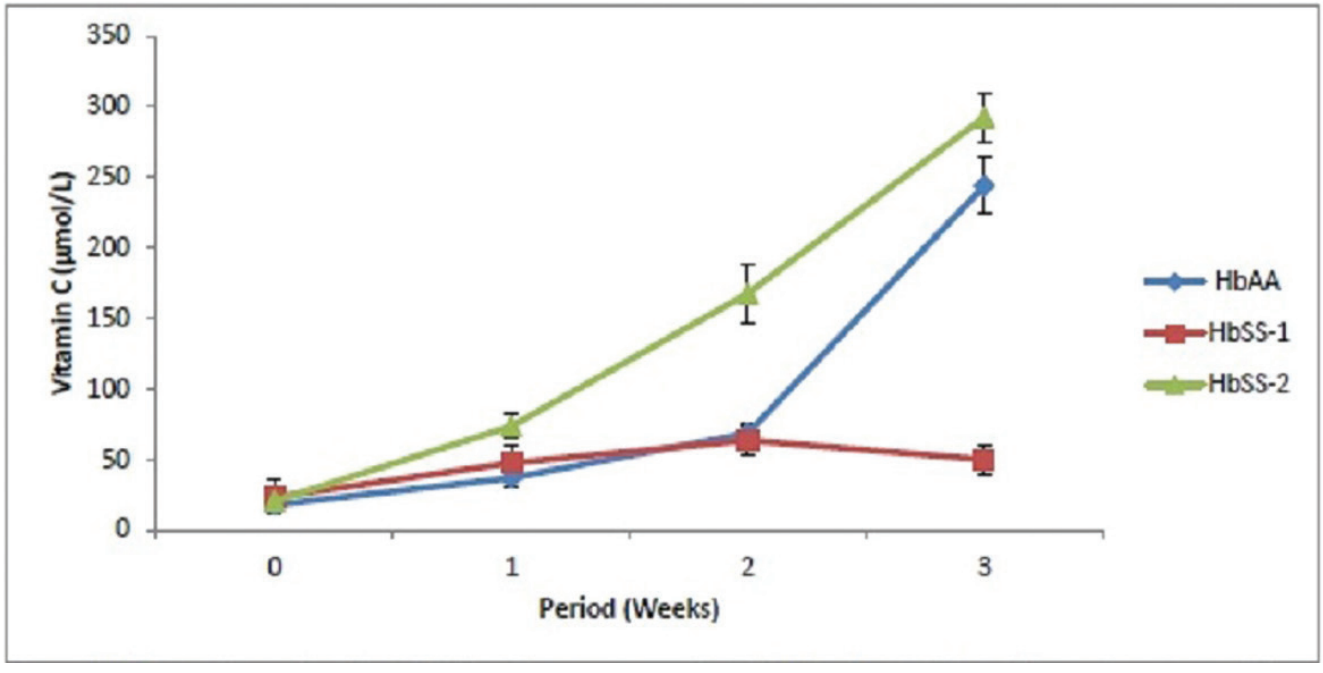

Figure 4.0: Effect of camel milk administration on serum vitamin C level of sickle cell anemia patients. Normal; HbAA: Control group, administerted with 10 ml/kg/day of fresh camel milk. HbSS-1: Sickle Cell Anaemic patients administered with 5 mg/day of folic acid and 100 mg/day of paludrine. HbSS-2: Sickle Cell Anaemic patients administered with 5 mg/day of folic acid and paludrine and 10 mL/kg/day of fresh camel milk.

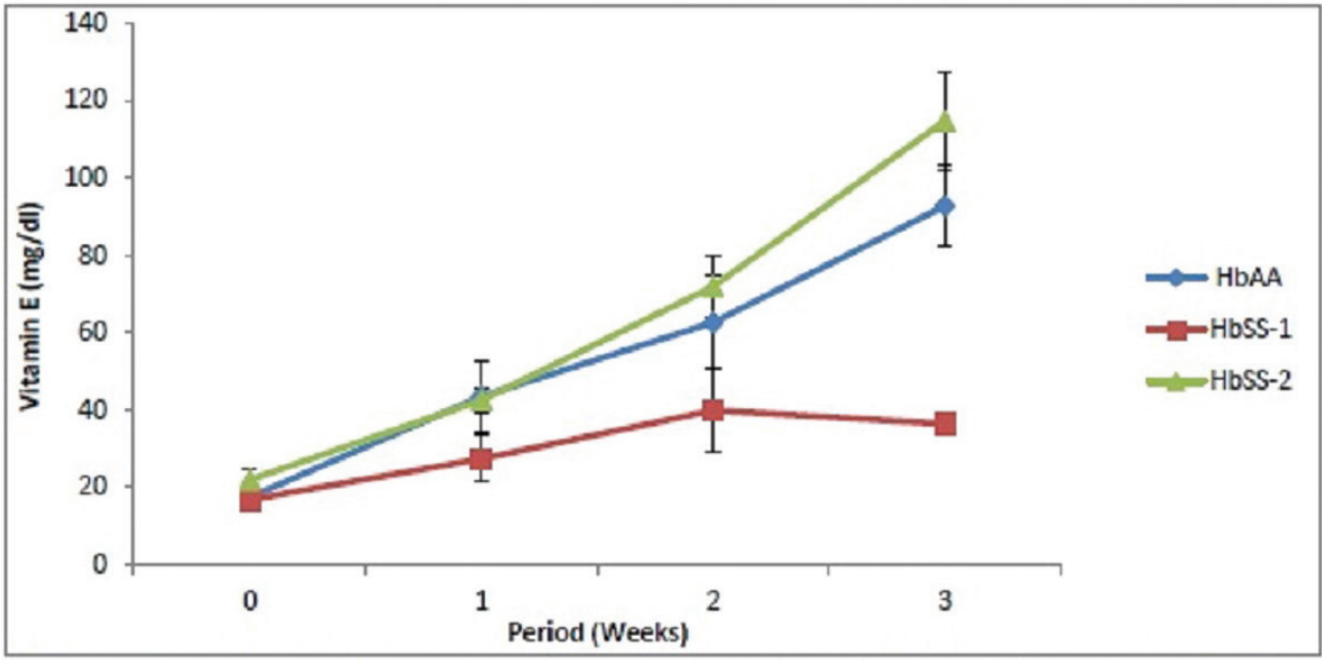

Figure 5.0: Effect of camel milk administration on serum vitamin E level of sickle cell anemia patients. Normal; HbAA: Control group, administered with 10 ml/kg/day of fresh camel milk. HbSS-1: Sickle Cell Anaemic patients administered with 5 mg/day of folic acid and 100 mg/day of paludrine. HbSS-2: Sickle Cell Anaemic patients administered with 5 mg/day of folic acid and 100 mg/day paludrine and 10 mL/kg/day of fresh camel milk.

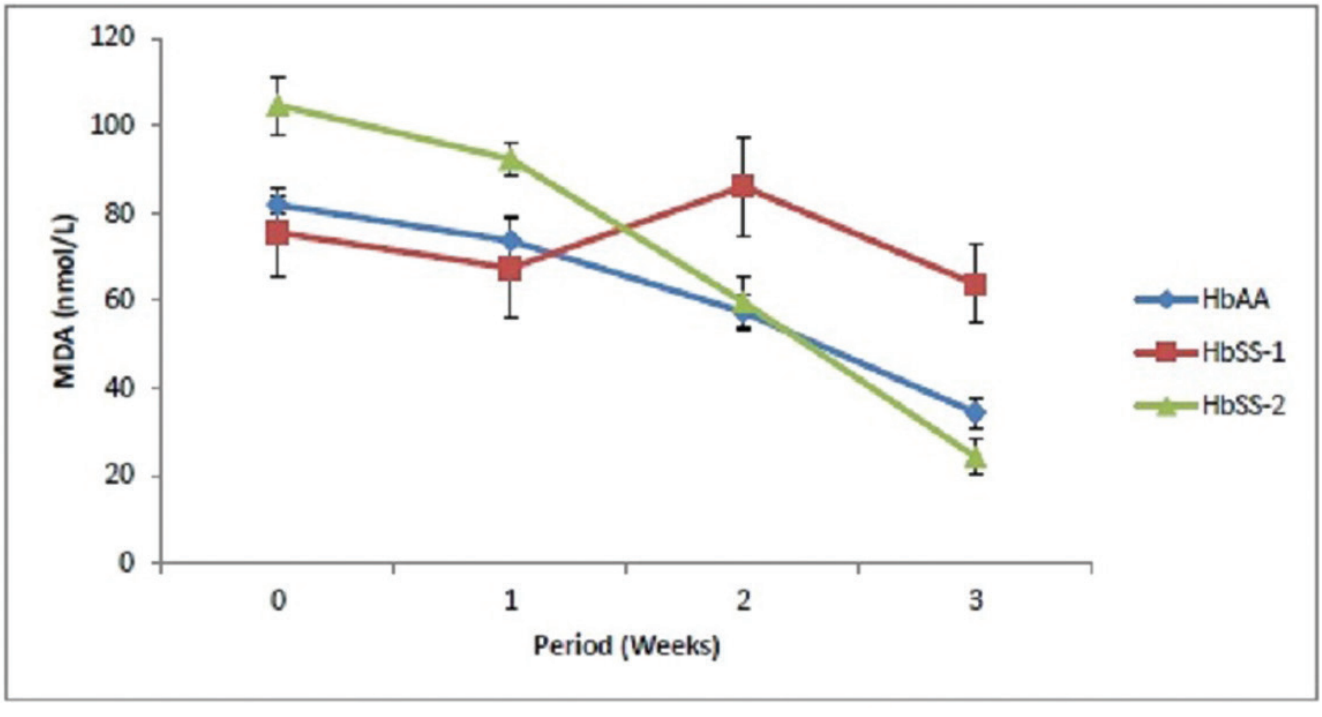

Figure 6.0: Effect of camel milk administration on serum MDA level of sickle cell anemia patients. MDA: Malondialdehyde, HbAA: Control group, administerted with 10 ml/kg/day of fresh camel milk. HbSS-1: Sickle Cell Anaemic patients administered with 5 mg/day of folic acid and 100 mg/day paludrine. HbSS-2: Sickle Cell Anaemic patients administered with 5 mg/day of folic acid and 100 mg/day of paludrine and 10 mL/kg/day of fresh camel milk.

indicating that the consumption of GSH may exceed its synthesis in SCA.

RBCs are protected from oxidative stress by intracellular antioxidant enzymes. In this study, SOD level was significantly increased in HbAA and HbSS-2 following camel milk administration; this could be attributed to the high contents of vitamin E, copper, and zinc of the milk. Production of sufficient amounts of SOD is achieved when the system gets adequate and balanced supply of vitamin E, Cu, and Zn [28]. In addition, Cu and Zn are cofactor of cytosolic SOD (SOD-1); therefore, the activity of this enzyme depends on the availability of Cu and/or Zn. The present findings are in conformity with that of Okot-Ais et al. [29] who reported that supplementation of vitamins C and E to sickle cell anemic patients resulted in increased SOD activity.

Hydrogen peroxide is reactive and detrimental byproduct that hampers normal metabolic processes, and causes damage to cells and tissues. Catalase is regularly worked in the cells to rapidly catalyze the breakdown of hydrogen peroxide into less-reactive and non-toxic gaseous oxygen and water molecules [30].

The increase in catalase activity may be associated to the high Fe content of camel milk which works as a cofactor for the enzyme. It was earlier observed that camel milk is rich in large quantity of iron among other minerals and vitamin [22].The increased catalase activity may also be associated with the peptides (RQ-8, LL-15, and YY-11) present in camel milk. These peptides were reported to increase catalase and SOD genes expression [31], hence increased both the synthesis and activity of catalase. The present result is in concord to the report of Hamed et al. [32] who reported that antioxidant enzymes activity increased due to camel milk supplementation in CCl4 intoxicated rats. Other previous studies demonstrated that the activity of catalase was reduced in HbSS patients compared to normal HbAA subjects [33,34].

Vitamin C has free radical scavenging activity. It directly accepts electron from superoxide hydroxyl anion and various other lipid hydroxyl peroxides. This study showed that vitamin C decreased significantly in HbSS-1 compared to HbAA and HbSS-2 subjects. The lowered vitamin C level in HbSS-1 patients indicates their exhausted status in its attempt to quench free radicals chain of reaction [33]. The increased concentration of serum vitamin C observed in HbAA and HbSS-2 compared to HbSS-1 may be attributed to the high levels of vitamin C in camel milk. In oxidative stress condition, vitamin C is drastically consumed, due to the fact it is used in regeneration of the reduced form of some powerful antioxidants such as GSH and vitamin E and thus stops the free radical chain reactions [35]. Regular administration of camel milk could compensate the depleted vitamin C and improved its serum level.

The increased concentration of vitamin E observed in HbAA and HbSS-2 in contrast to HbSS-1 may be attributed to the high levels of vitamin E content of camel milk and antioxidant sparing power of camel milk. The result of DPPH radical scavenging power of camel milk peptides earlier reported by Masoud et al. [36] is an evidence that the milk is potent antioxidant and its consumption may spare other antioxidant molecules such as vitamin E from the use against cellular oxidation. This work has corroborated some earlier studies that found depletion of vitamin E in SCA patients [37,38].

MDA is a good indicator for oxidative damage. The present findings showed that MDA concentration significantly decreased in HbAA and HbSS-2 following 3 weeks administration of camel milk. This could be linked to the antioxidant potential of camel milk. Our previous report suggested that camel milk is effective in reversing the lipid peroxidation as evidence by significant decrease in serum MDA level in hypertensive rats [39]. Chronic hemolysis experienced by sickle cell anemic patients is linked to shorter lifespan of RBC and cellular oxidative stress [40]. HbSS oxidizes at 1.7 times than the HbAA, this results to increased production of superoxides radicals and formation of hydrogen peroxide. Hydrogen peroxide generated will in turn produce hydroxyl radicals that damage the RBC membrane, proteins, and lipids. MDA is produced due to the oxidative degradation of arachidonic acid and polyunsaturated fatty acids of cell membranes. It is therefore not surprising to notice increased MDA level in HbSS-1 compared to HbSS-2. However, the latter was given camel milk in addition to routine prophylactic SCA drugs, and the milk is rich in antioxidant molecules that prevent cellular oxidation thereby reducing the serum level of MDA.

Conclusion

Three weeks administration of camel milk resulted in an increased serum level of GSH, antioxidant vitamins C and E and improved antioxidant enzymes activity as well as decreased MDA level. Thus, regular consumption of the milk could relief

the complication usually experienced by sickle cell anemic patients.

Recommendations

It is recommended that more large-scale studies on the chemical composition and clinical benefits of camel milk should be conducted both locally and nationally in order to further substantiate the observed benefits of camel milk in the management of sickle cell patients.

It is also recommended that Sokoto State Government should liaise with the management of Specialist Hospitals Sokoto and camel herds and open a centre in the state where the less privilege sickle cell anemic patients will collect camel milk at regular interval. The center should also be charged with the responsibility of enlighten the patients on the benefit of using the milk.

Ethical approval

All experiments have been examined and granted approval by Ethics Committee of Specialist Hospital Sokoto.

Competing Interests

Authors have declared that no competing interests exist.

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