Review Article

Association between Sickle Cell Anemia and Malaria: A Systematic Review

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ABSTRACT

Background: Sickle cell disease (SCD) is a hereditary illness that is prevalent in malaria-prone locations. In these endemic locations, it has historically been linked to high rates of childhood death. This shows that SCD patients with malaria should start effective anti-malarial medication very away. Proguanil was a suitable chemoprophylaxis treatment for these individuals to reduce the prevalence of asymptomatic parasitization and avoid malaria. Sulphadoxine-Pyrimethamine Intermittent Preventive Treatment (IPT) has also demonstrated significant promise in lowering malaria and anemia incidence. Additionally, hydroxyurea is a successful therapy for sickle cell anemia. This article generally discusses the main association between sickle cell anemia and malaria and outlines the related therapies.

Method: For pertinent information, PubMed, Web of Science, Science Direct, Cochrane Library, and Google Scholar were scoured in-depth. The Rayyan QRCI was employed throughout this thorough procedure.

Results: our study article included 18 studies, in which the effect of sickle cell anemia in the presence of malaria was explained. The main parameters like age, sex, type of drug and time to use were obtained. Clinical studies were required to determine the relation between sickle cell anemia and malaria and determine the effective therapy.

Conclusion: people with sickle cell anemia (SCA), the most severe type of SCD, are more likely to die from malaria than persons with SCT or no hemoglobin gene variation.

Keyword: Sickle Cell, Malaria, Plasmodium Falciparum, Hemoglobin, Anemia, Hydroxy urea.

Introduction

WHO estimates says there were 435,000 instances and 219 million cases of malaria worldwide in 2017 fatalities that were directly related to the disease [1]. Malaria is still a leading cause of illness and mortality, 67% of all childhood deaths are among youngsters, especially [1]. This is true even though it ceased to exist position as the leading cause of mortality in Cameroon. Every two minutes, Malaria kills a little toddler in sub-Saharan Africa and other epidemic regions [2]. Hemoglobinopathies may offer protection Against malaria's severe, life-threatening symptoms [3]. The most significant of them is the sickle cell disease (SCD) mutation, which reduces children's risk disease-causing Plasmodium falciparum malaria by 90% African sub-Saharan region. a single-site change in the globin gene causes valine to replace Position 6 of the peptide contains glutamic acid, causing sickle cell disease, a hereditary chronic hematological illness [4]. SCD is a serious public health problem that mostly affects tropical countries, especially in sub-Saharan

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Africa. As per the World Health Organization (WHO), According to estimates, 300,000 babies are born each year with SCD, Sub-Saharan Africa accounts for 75% of them. The gene does not offer immunity to parasitic malaria, but it does stop illness from developing after infection [5]. One could anticipate that the relative malaria protection provided by sickle cell trait would be at least as strong in the homozygous condition (SS). Clinical observations have revealed it to be riskier, though, as malaria not only makes preexisting anemia in SCD patients life-threatening, but also makes it more difficult for them to eliminate parasites from their RBCs due to aberrant splenic function. Malaria is a significant factor in the early death of SCD patients in Africa [6]. Even worse, malaria is the most common parasite illness that affects people and kills more children than any other infectious disease worldwide. This has unmistakably supported the theory that the pressure caused by the malaria parasite is a major driving force behind this change. Currently, it is widely known that P. falciparum may choose genes that lead to resistance and is an evolutionary force that has affected the human genome. It is thought that a gene gives a survival benefit whenever it is very prevalent in the population and can reduce fitness [7]. The majority of kids with sickle cell anemia never get a thorough diagnosis, simple vaccinations that can save lives, owing to a lack of newborn screening programs and proper clinical treatment, or antibiotic prophylaxis; it is estimated that 50 to 90% of these children will pass away before turning five years old [8]. For sickle cell anemia, an oral medication with proven laboratory and clinical efficacy is hydroxyurea [9]. In addition to inhibiting erythrocyte sickling by inducing fetal hemoglobin, hydroxyurea has positive effects on leukocytes, reticulocytes, and the endothelium. Hydroxy urea improves laboratory variables and lowers clinical problems, particularly when the dosage is increased to the maximum tolerable level [10]. The viability, in two investigations, the benefits and safety of hydroxyurea for children with sickle cell anemia in sub-Saharan Africa were established [11]. The NOHARM project (Novel Use of Hydroxy-urea in a Malaria-Prone African Region) study that was placebo-controlled and double-blinded, and showed that conventional fixed-dose hydroxy-urea (20 mg daily for each kilogram of body weight) was safe for use among infants and toddlers with sickle cell anemia while also providing all anticipated therapeutic benefits [12]. Realizing Effectiveness across Continents with Hydroxy-urea is known as REACH, In four African countries, a study using open-label hydroxyl-urea that escalated to the maximum tolerable dosage was conducted. This experiment indicated not only dramatically decreased occurrences of malaria, transfusions, and mortality in this high-risk population but also the safety and therapeutic benefits of hydroxyurea in children with sickle cell anemia [13]. Proguanil, sulfadoxine-pyrimethamine with amodiaquine (SP-AQ), and dihydroartemisinin-piperaquine (DP) were three more very successful chemoprevention regimens that were examined in Kenyan children with SCA. The gold standard of care is daily proguanil, monthly SP-AQ is effective for chemoprevention of seasonal malaria, DP is also quite effective as a therapeutic and, in studies, as a monthly preventative measure in youngsters [14] and expectant mothers [15]. In order to protect patients with confirmed SCA from clinical malaria and unfavorable hematologic results, this article reports the association between sickle cell anemia and malaria, and examines effective therapies to control the disorder.

Methods

For this systematic study, The PRISMA acronym stands for favored Reporting Items for Systematic Reviews and Meta-analysis) recommendations were adhered to.

Study Design and Duration: This methodical review was completed in August of 2023.

Search Technique. A complete search was conducted in five significant databases, such as Google Scholar, Web of Science, PubMed, and Science straight, and EBSCO, to find the pertinent studies. Our search was restricted to English, and we took into consideration the specific requirements of each database. In order to discover relevant research, the next keywords were changed into terms for PubMed Mesh: "Sickle cell, Malaria, Plasmodium falciparum, Hemoglobin." To match the key phrases, the Boolean operators "OR" and "AND" were applied. Publicly accessible articles, human trials, and publications the search results met everything in English.

Selection criteria. Inclusion criteria: For this review, we took consideration of the following factors:

- Any research investigates the association between the sickle cell disease and malaria
- There were no restrictions on age.

• Accessible, free articles.

Exclusion criteria:

• We disqualified individuals who had a history of coma, head injury, cerebral palsy, developmental delay, or known chronic illnesses needing medical attention.

• Letters to the editors, case reports, and responses to controversies were not included.

• Foreign language.

Get the data

To discover duplicate results from the search technique output, Rayyan (QCRI) was employed. The scientists used a set of inclusion/exclusion standards to filter evaluating the significance of the titles and abstracts based on the aggregated search results. All manuscript that satisfies the prerequisites for admission has undergone a thorough evaluation by the reviewers. After careful consideration, the authors offered alternative strategies for settling disagreements. The studies' names, authors, study year, nation, participants, gender, drug dose, key findings, and conclusion were all made available to the writers.

Method for synthesising data: To give a qualitative summary of the research's results and main elements,Utilizing information from pertinent studies, summary tables were created. Once the data from the systematic review was retrieved, the most effective way to use the data from the included study articles was determined.

Risk of bias evaluation: Using the ROBINS-I risk of bias assessment approach for non-randomized trials of treatments, the caliber of the included studies was assessed. The seven themes that were assessed were confounding, participant selection for the research, categorization of interventions, deviations from intended interventions, missing data, evaluation of outcomes, and choice of reported result.

Results

Search outcomes: A thorough search turned up 510 study articles, 60 of which were duplicate. After screening the titles and abstracts of 450 investigations, 135 papers were rejected. Out of 315 reports that were looked up for recuperation, only 165 could not be located. 150 publications were eventually screened for full-text review; 130 were disqualified owing to flawed study findings, and four were disqualified due to the wrong population type. In this systematic review, 16 relevant study articles were included. (Figure 1) displays an overview of the study selection procedure.

Characteristics of the research that were included: The sociodemographic details of the studies that are included are listed in (Table 1). Our results included 18 studies. Seven of them were conducted in Africa as it is the most epidemic area [22- 26, 11, 29], two of them were conducted in Tanzania [16, 28], one in Uganda [17], one in Ghana [27], and one in Kenya [7]. The majority of the studies focused on children [7,16,17,18,21,23,24,25,26,27]. Additionally, one study was conducted with pregnant women [19], and another included both adults and children [20]. (Table 2) includes the mean information of drug which used. In studies [11, 23, 24, 29], oral hydroxyurea was administered daily at a dosage of 20 mg per kilogram. Meanwhile, in [20, 26] studies, the Proguanil and Sulphadoxine-Pyrimethamin were used. The study used Artesunate-amodiaquine and Artemether-lumefantrine [27]. (Table 3) presents the clinical characteristics of the included studies. It could be concluded that malaria contributes significantly worsen the SCA patients [16, 7, 18, 21] particularly in delivered women [19] , making it critical that they are safeguarded by treatments such as hydroxyurea which is practical and secure for a sickle cell disease patients who reside in endemic areas[11, 23, 24, 29] , and similar to Proguanil and Sulphadoxine-Pyrimethamin, which are well-tolerated and have been shown to lower Dactylitis prevalence with asymptomatic P. falciparum infection "malaria" [20,26].

Discussion

Numerous gold medals are mentioned in the history of sickle cell anemia (SCA). First, almost 50 years ago, SCA was the reason the phrase "molecular disease" was first used, which gave rise to the idea of "hemoglobinopathies" [30]. Second, it when the structural abnormality of hemoglobin (Hb) S was discovered, it was the first time a single amino acid alteration in a protein was shown to cause a serious sickness [31]. Third, after the three-dimensional structure of Hb was uncovered, it became clear why Hb S had the odd characteristic of being normal when oxygenated but abnormal when deoxygenated [32]. Fourth, a polymorphic DNA location was found to be in linkage disequilibrium with the sickle mutation, a restriction fragment length polymorphism (RFLP), originally known as a single nucleotide polymorphism (SNP), has changed its name.

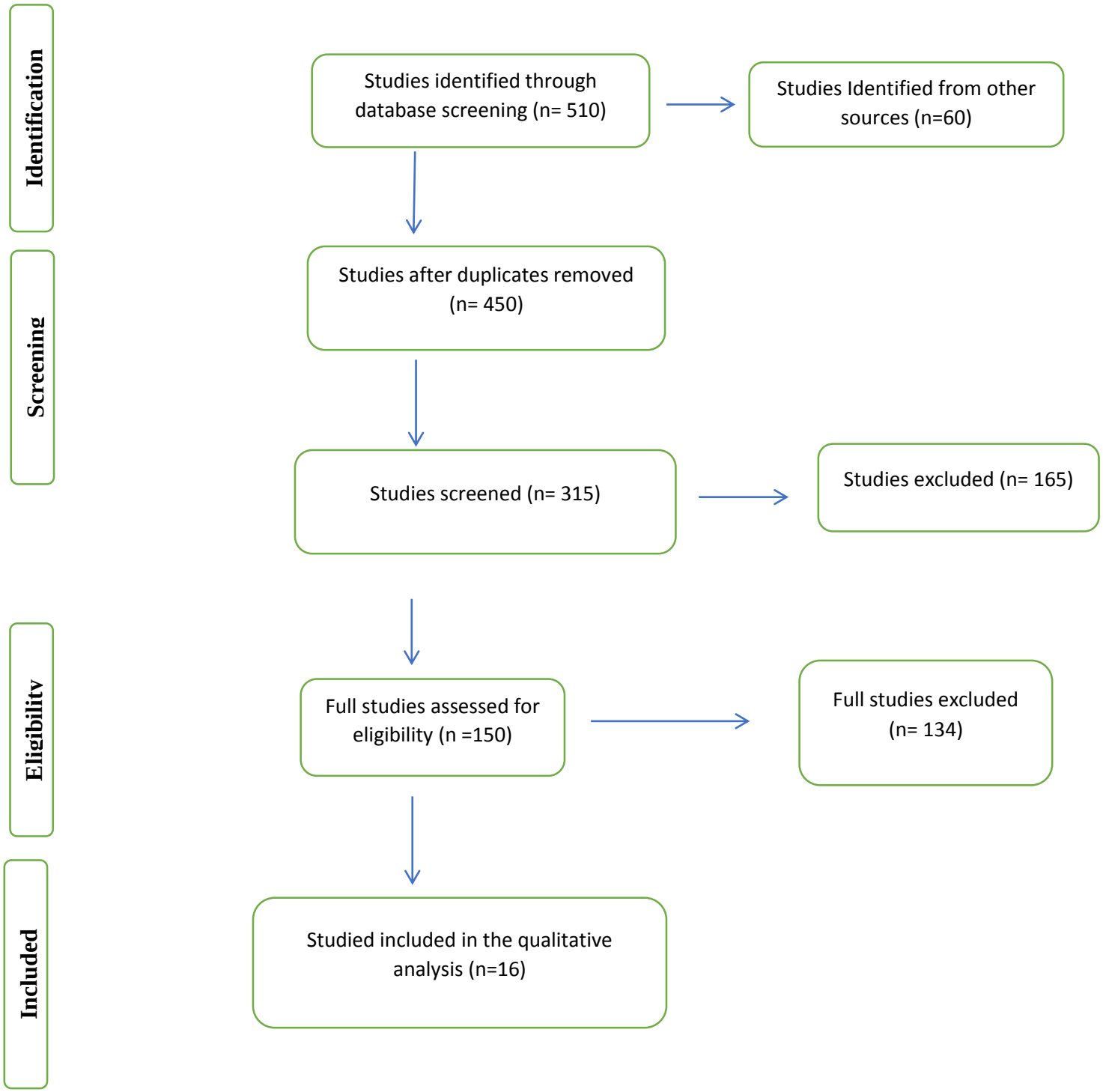

Figure (1): PRISMA flowchart summarizes the study selection process.

Table (1): Socio-demographic characteristics of the included participants.

Study	Country	Study design	Patients	Gender	Age range	Period of study
Croke, Kevin et al. 2017 [16]	Tanzania	NA	767	56% female	15.9 years	January 2006 to December 2013
Kosiyo, Paul et al. 2022 [7]	Western Kenya	cross-sectional study	217	NA	1–192 months	April 2018 and February 2019
Oppong, Mavis et al.2020 [17]	Volta region	Cross-sectional community-based survey	938 samples	52.6% females	6.4±3.4 years	NA
Henrici, Ryan C et al. 2021 [18]	Uganda	NA	267	NA	18 months to 12 years	November 2008 to December 2013
Patel, Jaymin C et al.2016 [19]	Malaw	cross-sectional survey	NA	NA	Delivered women	November 2009 and January 2011
Dawam, J A et al. 2016 [20]	Nigeria	NA	114 children 40 adults	NA	NA	3 months
Lopera-Mesa, Tatiana M et al. 2015 [21]	Maliin	prospective cohort study	NA	NA	0.5–17 years	2008-2011
Maitland, Kathryn et al. 2021 [22]	Africa	NA	3196	NA	NA	NA
McGann, Patrick T et al. 2018 [23]	sub-Saharan Africa	prospective open label trial	NA	48.8% females	1–10 years	30-month

Tshilolo, Léon et al. 2019 [24]	sub-Saharan Africa	NA	606	NA	1 to 10 years	NA
Uyoga, Sophie et al. 2022 [25]	Africa	post-hoc secondary analysis	3944	NA	2 months to 12 years	Sept 17, 2014, and May 15, 2017
Taylor, Steve M et al. 2022 [26]	East Africa	open-label, parallel assignment randomized trial	246	53.3% boys	4.6 ± 2.5 years	January 23, 2018, and December 15, 2020
Adjei, George O et al. 2014 [27]	Ghana	NA	60	NA	six months to 12 years	January 2010 and December 2011
Opoka, Robert O et al. 2017 [11]	sub-Saharan Africa	randomized, double-blinded, placebo-controlled trial	208	NA	NA	24 September 2014 and 2 October 2015
Saidi, Hamza et al. 2016 [28]	Tanzania	cross-sectional study	124	58.1% male	Less than 15 years old	August 2012 and September2012
John, Chandy C et al. 2020 [29]	sub-Saharan Africa	randomized, double-blind trial	187	NA	NA	NA

Table (2): Clinical characteristics and outcomes of the included studies.

Study	Procedures	Outcomes
Croke, Kevin et al. 2017 [16]	Children were chosen from a list of those who had undergone SCT screening. Community health workers kept an eye on the prevalence of malaria and febrile fever.	Malaria protection has been discovered to be provided by sickle cell trait.
Kosiyo, Paul et al. 2022 [7]	Haematological parameter differences were examined between groups using the Mann Whitney U test and between groups using the Kruskal Wallis test.	Congenital haematological abnormalities,of which sickle cell disease is one of the best examples, can cause variations in blood cell counts and their associated characteristics. Additionally, these modifications have frequently been seen in malaria.
Oppong, Mavis et al.2020 [17]	The list of all the districts in each zone was gathered and one district was randomly chosen from each zone as part of a multi-stage sampling method.	5.5 % of the children had microscopic Plasmodium falciparum parasitaemia, while 14.2% had sub-microscopic prevalence, according to PCR.
Henrici, Ryan C et al. 2021 [18]	comparison of host responses to P falciparum between children with SCA and normal	Children without scikle cell anaemia and those with severe anaemia and P falciparum parasitemia shared clinical traits during severe malaria, but those with scikle cell anaemia had widely decreased parasite biomass and inflammatory mediators.
Patel, Jaymin C et al.2016 [19]	Polymerase chain reaction was used to identify parasites in placentas and peripheral blood of postpartum women. Placentas were also evaluated histologically for PM	HbAS did not offer defence against placental malaria or its effects.
Dawam, J A et al. 2016 [20]	Patients with sickle cell disease were randomly assigned to receive either daily Proguanil or monthly Sulphadoxine-Pyrimethamine for the prevention of malaria. Over a period of three months, each monthly clinic visit included the active detection of the malaria parasite in the peripheral blood and packed cell volumes.	Monthly Sulphadoxine-Pyrimethamine chemoprophylaxis reduced the incidence of asymptomatic malaria parasitaemia more effectively than daily Proguanil,
Lopera-Mesa, Tatiana M et al. 2015 [21]	NA	The population's gender distribution, ethnic composition, and prevalence of these RBC variations generally reflected southern Malian populations.
Maitland, Kathryn et al. 2021 [22]	The neighbourhood blood transfusion services (BTS) provided blood transfusions using three different blood component types: whole blood, packed red cell concentrates, and gravity-produced red cell concentrates, among others	Children with SCD may not require an urgent transfusion, while children with severe and complex anaemia who are not feverish may get larger amounts of blood instead.

McGann, Patrick T et al. 2018 [23]	Participants had a two-month screening process to ensure they were eligible for the study's therapy.	REACH confirms the feasiblety to administer hydroxyurea to SCA patients in a way that is both safe and effective
Tshilolo, Léon et al. 2019 [24]	NA	The hydroxyurea therapy proved practical, relatively safe, and beneficial in both the laboratory and the clinic.
Uyoga, Sophie et al. 2022 [25]	Children with severe anaemia in four hospitals were included in the TRACT experiment . Following batch-genotyping by PCR at the conclusion of the study, children were categorised as normal (HbAA), heterozygous (HbAS), or homozygous (HbSS; SCA) for the rs334 AT sickle mutation in HBB.	People with SCA are more likely to die at day 28 than people without SCA in general.
Taylor, Steve M et al. 2022 [26]	Receive either daily Proguanil, monthly SP-AQ, or monthly DP in a 1:1:1 ratio in an open-label setting.	Although monthly DP did considerably lower the rate of asymptomatic parasitization, neither monthly SP-AQ nor monthly DP decreased the incidence of the primary endpoint clinical malaria when compared to proguanil. Children receiving monthly DP saw a substantial decrease in dactylitis, and hematologic results were frequent.
Adjei, George O et al. 2014 [27]	Children with SCD with acute uncomplicated malaria were randomly assigned to either artesunate-amodiaquine (AA) or artemether-lumefantrine (AL) therapy, but non-SCD children with simple malaria were not.	These indicators did not differ between AA- and AL-treated patients.
Opoka, Robert O et al. 2017 [11]	Folic acid, penicillin prophylaxis, and pneumococcal immunisation were all part of the routine treatment for SCA given to all subjects. Children got insecticide-treated mosquito nets and monthly sulphadoxine pyrimethamine as part of their malaria prophylaxis.	Children given hydroxyurea had considerably higher haemoglobin concentrations and foetal haemoglobin, as well as lower leukocytes and reticulocytes.
Saidi, Hamza et al. 2016 [28]	After obtaining parental or guardian written consent, a trained research assistant interviewed the parent or guardian and filled out a questionnaire with demographic data, the cause of hospitalization, the lifetime prevalence of experiencing SCA complications, and previous treatments.	Avaso-occlusive episode was a side effect of SCA in 121 individuals. Stroke in 21 subjects and acute chest symptoms in 83 patients. 17 of the 21 participants who got a stroke diagnosis also mentioned having experienced seizures in the past.
John, Chandy C et al. 2020 [29]	Compared to 37% of the kids in the fixed-dose group, 86% of the kids in the dose-escalation group had surpassed the primary-outcome criteria.	Children in the dose-escalation group experienced fewer hospitalizations, transfusions, acute chest syndrome or pneumonia episodes, unfavorable sickle cell events, and vaso-occlusive pain crises.

Table (3): Drug characteristics of the included studies.

Study	Type of drug	Dose	
Croke, Kevin et al. 2017 [16]	NA	NA	NA
Kosiyo, Paul et al. 2022 [7]	NA	NA	NA
Oppong, Mavis et al.2020 [17]	NA	NA	NA
Henrici, Ryan C et al. 2021 [18]	NA	NA	NA
Patel, Jaymin C et al.2016 [19]	NA	NA	NA
Dawam, J A et al. 2016 [20]	Proguanil	NA	Daily
	Sulphadoxine-Pyrimethamin		Monthly
Lopera-Mesa, Tatiana M et al. 2015 [21]	NA	NA	NA
Maitland, Kathryn et al. 2021 [22]	NA	NA	NA
McGann, Patrick T et al. 2018 [23]	hydroxyurea	NA	NA
Tshilolo, Léon et al. 2019 [24]	hydroxyurea	17.5±1.8 mg per kilogram	dose per day
Uyoga, Sophie et al. 2022 [25]	NA	NA	NA
Taylor, Steve M et al. 2022 [26]	Proguanil.	NA	Daily
	sulfadoxine/pyrimethamine-amodiaquine (SP-AQ).	NA	monthly
	dihydroartemisinin-piperaquine.	NA	Monthly

Adjei, George O et al. 2014 [27]	Artesunate-amodiaquine	25 mg / 67.5 mg), one tablet/dose, 4.5–9 kg. One tablet/dose (50 mg/135 mg) for 9–18 kg. 100 mg/270 mg), one tablet/dose, for ages 18 to 36 kg. 100 mg/270 mg), two tablets per dosage, 36 kg.	single daily dose for three days according to body weight
	Artemether-lumefantrine	1 tablet/dose for 5-14 kg. Two pills per dosage, 15–24 kg. Three pills per dosage, 25-34 kg. Over 35 kg: four tablets/dose.	according to body weight for the first day at zero and eight hours, and then twice daily for the next two days
Opoka, Robert O et al. 2017 [11]	oral hydroxyurea	20 ± 2.5 mg/kg for 12 months	once daily
Saidi, Hamza et al. 2016 [28]	NA	NA	NA
John, Chandy C et al. 2020 [29]	Hydroxyurea	20 mg per kilogram	once daily

This was the key discovery that underpinned all recent genome-wide association studies (GWAS). As a result, SCA has contributed significantly to the study of human molecular genetics [33]. At the same time, SCA is a significant section of hemolytic anemia in terms of hematology. So, we concentrated on the intersection between malaria, an infectious disease, and SCA, a blood disorder. The connection is intricate. SCA's epidemiology has been significantly impacted by malaria, and malaria's clinical course is influenced by SCA. In this experiment including children with sickle cell anemia, we discovered that hydroxy-urea therapy was practicable, relatively secure, and offered benefits in the clinical and laboratory. In particular, after a year of hydroxy-urea treatment, the frequency of medical events, for instance, vascular painillness, malaria, Death, transfusion, and, decreased in comparison to pretreatment rates. Hydroxy-urea has become well-known as a strong, disease-modifying medication in both the United States and Europe, having regulatory clearance for usage in both children and adults. Although fetal hemoglobin induction is the main method by which hydroxyurea works, this medication also has numerous beneficial impact on leukocytes and erythrocytes, making it a potent oral remedy for this life-threatening illness. And even endothelium, particularly when administered at the highest tolerable dosage [34]. WHO includes hydroxyurea as an essential medicine for treating sickle hemoglobinopathies in both children and adults [35], which encourages its extensive usage on a worldwide basis. However, there hasn't been many research done in low-income areas like sub-Saharan Africa, where the illness sickle cell most commonly occurs. The NOHARM experiment, which was conducted at a single, major malaria-endemic region in Africa, urban location in Uganda, as well as a number of minor hydroxy-urea investigations carried out in Nigeria [36], shown that hydroxy-urea did not increase malaria incidence compared to placebo [37]. The REACH study's participants lived in both urban and rural areas of Africa where the frequency of malaria is noticeably higher than in Kampala. The total incidence of malaria in the NOHARM study was surprisingly low. Despite Uganda, it is the location where the experiment was conducted [24]. Daily Proguanil, monthly amodiaquine/sulfadoxine/pyrimethamine, and monthly piperaquine/dihydroartemisinin all markedly reduced the prevalence of asymptomatic parasitization, but none of these therapies significantly decreased occurrence of the main result, clinical malaria. We saw a substantial decrease Children getting monthly dihydroartemisinin piperaquine for dactylitis, and hematologic results were frequently reported. In order to shield kids with SCA from hematologic and parasitological morbidity, Due to its proven safety, monthly administration of dihydroartemisinin piperaquine is a potential and useful option, the high rate of adherence among our subjects and its well-proven high effectiveness in preventing malaria [26]. Hematology and infectious disease medicine continue to face formidable obstacles from malaria and sickle cell anemia, respectively. Both conditions pose serious threats to the public's health. One may have thought that after learning about the benefits of AS heterozygotes with regard to malaria, we would be able to shield others from contracting the disease as well. We can yet hold out hope that the strength of mutation and selection in biological evolution will be matched by creative human solutions. Patients continue to suffer greatly from SCA in the interim, particularly in underdeveloped nations where the prevalence is shocking. It is critical that more be done to provide giving these patients a higher standard of living. This should incorporate efficient pain management, typically, hydroxy-urea, typically, hydroxy-urea.

Conclusion

Sickle cell anemia is a significant subgroup of hemolytic anemia, and at the same time, its epidemiology is a striking marker of Plasmodium falciparum malaria's history and current global spread. The connection between this blood disorder and this infectious illness was the main topic. Individuals with sickle cell anemia (SCA) are especially at risk for malaria's fatal effects. The easiest explanation for this phenomenon is that malaria makes the anemia brought on by SCA worse. In malaria-endemic countries, it is crucial from the standpoint of public health that SCA patients, as well as kids, are safeguarded against malaria by suitable treatment. Monthly SP-AQ exhibited no discernible advantage over daily Proguanil, while daily hydroxy-urea therapy was both safe and practical for kids with sickle cell anemia. Additionally, hydroxy-urea therapy decreased the frequency of unpleasant events, infections, malaria, transfusions, and fatalities.

Conflict of Interest

None

Funding

None

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