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Malaria Prevention in Children with Sickle Cell Disease: A Review of Options

A.A. Abdulkarim
Department of Paediatrics, University of Ilorin Teaching Hospital, Ilorin, Kwara State, Nigeria

Abstract: Malaria remains a major source of morbidity and mortality in the tropics and subtropics. In Nigeria where the disease is endemic, sickle cell disease is also common. Malaria precipitates crises in patients with sickle cell anaemia and its prevention in this group of patients is of paramount importance to both the clinician and public health practitioner. Many cost-effective prevention options are now available for malaria and these can be deployed in sickle cell anaemia in order to improve the health of those affected.

Key words: Malaria prevention, sickle cell disease, options

INTRODUCTION

Sickle Cell Disease (SCD), a monogenic, inherited blood disorder with a wide phenotypic heterogeneity and equally wide clinical spectrum is the commonest severe hereditary condition in Africa. It also occurs in the Mediterranean, Caribbean and the Middle Eastern regions (Fleming *et al*., 1979; Hoffbrand *et al*., 2002; Aidoo *et al*., 2002). SCD occurs when an individual inherits abnormal (S) genes responsible for the production of haemoglobin from both parents i.e., autosomal recessive (Fleming *et al*., 1979; Hebbel, 2003).

The frequency of SCD varies in different population. About 3-4% of the populations in sub-Saharan Africa are homozygous for SCD. Two common genotypes of the disorder occur, homozygous sickle cell disease (also known as sickle cell anaemia) where, the S gene is inherited from both parents and sickle cell/haemoglobin C disease where, an individual gets one S gene from a parent and a C gene from the other. In Nigeria, 1:300 have SCA i.e., homozygous for the S haemoglobin, while 1:500 have sickle cell/haemoglobin C disease out of its estimated 120 million people. The prevalence of the carrier state for the S gene is up to 25%. The gene for alpha thalassemia occurs frequently with the S gene among Nigerians giving rise to the S thalassemia disorder (Hoffbrand *et al*., 2002; Fleming *et al*., 1979; Begue and Castello-Herbreteau, 2001).

The distribution of the S gene has been postulated to be an evolutionary protective mechanism against malaria infection and it parallels that of the malaria in Africa. Those with one abnormal S haemoglobin i.e., sickle cell trait have some protection against malaria, while those with the homozygous condition are at higher risk of malaria mortality and morbidity (Begue and Castello-Herbreteau, 2001; Hills *et al*., 1991; Weatherall and Clegg, 2001; Greenwood *et al*., 2005; Serjeant and Sergeant, 2001; Serjeant, 2005).

Malaria, a common disease in the tropics and subtropics, is the most important parasitic infection in public health and has the greatest impact in children in Africa (Greenwood *et al*., 2005; Oniyangi and Omari, 2003). The disease is responsible for more than a million deaths annually most of it in Sub-Saharan Africa and it also has enormous economic and social costs. Over 90% of those affected are children under 5 (Greenwood *et al*., 2005). Most deaths are due to severe forms of the disease by *P. falciparum* in the form of severe anaemia, cerebral malaria and respiratory acidosis. In Nigeria, transmission occur all year round (stable malaria) with wide variation depending on the part of the country concerned. The severe forms of the disease only affect children below 5 pregnant women primigravidae and those with no or low immunity to malaria such as travellers (Greenwood *et al*., 2005).

In areas of the world, where malaria exists it modifies the clinical presentation of SCD and is associated with increased mortality and morbidity in the homozygous states where it can precipitate vasooclussive and anaemic crises (Serjeant, 2005; Oniyangi and Omari, 2003; Juwah *et al*., 2004). Heterozygous haemoglobin S appears to make the carriers less likely to have a high density of malaria parasite and also to develop severe forms of malaria although the precise mechanism by which it does this is unclear. Postulated mechanisms include reducing replication or enhancing clearance of the parasites (Kaine, 1983; Fleming, 1989; Juwah *et al*., 2004; Serjeant, 2005). There is little research in Africa on SCD and the prevention of mortality and morbidity from it. Meanwhile, malaria control remains a priority project to advance

public health but there are enormous challenges to its control in Africa (Greenwood *et al*., 2005). The programme in Nigeria is focused on reducing mortality and morbidity from the disease by prompt treatment and multi-pronged prevention including the use of preventive treatment in pregnancy and roll out of Insecticide treated nets.

The prevention of malaria among those who are at high risk of death or serious morbidity such as pregnant women is practiced in many parts of the world where malaria is common (Oniyangi and Omari, 2003; Greenwood *et al*., 2005). One group at high risk for malaria is those with Sickle Cell Anaemia (SCA) and although malaria prevention is widely used among this group there is little evidence base for the current practices in Nigeria (Akinyanju, 1989; Oniyangi and Omari, 2003; Okunoghae *et al*., 1992; Juwah *et al*., 2003).

The increased mortality and morbidity among SCD individuals that are attributable to malaria are potentially preventable with available tools such as Insecticide Treated Nets (ITNs), chemoprophylaxis and the use of Intermittent Preventive Treatment (IPT). This study enumerates available cost-effective interventions that can be used in sickle cell disease patients to reduce the burden of malaria.

Interactions between SCD and malaria: The evolution of SCD in Africa has been linked to the pressure to protect the individuals against malaria which is a common and at times severe infection in the region and evidence show that the S trait offers protection against malaria and this increases with age. The higher prevalence of the S gene in these parts of the world illustrates the selective pressure of malaria (Hoffbrand *et al*., 2002; Fleming *et al*., 1979; Akinyanju, 1989; Buchanan *et al*., 2004).

SCD individuals can have crises precipitated by malaria and bacterial infections e.g., pnuemococcal, to which they are highly susceptible because of impaired immune function and functional asplenia (Fleming *et al*., 1979; Okunoghae *et al*., 1992; Akinyanju, 1989). These factors are perhaps the most important ones considering many developing countries where the S gene is highly prevalent. Evidence suggests that malaria, probably due to fever and dehydration, is in fact the most common precipitating disease in malaria endemic areas as in much of Africa (Harrison, 1982; Serjeant *et al*., 1994; Gendrel *et al*., 1992; Diop *et al*., 1997). It has been implicated in many cases of hyper-haemolytic anaemia and the association has been clinically observed in many series. Between 25 and 50% of fevers among homozygous SCD or Sickle Cell Anaemia (SCA) patients in some parts of Africa is caused by malaria while about 20% of Severe Anaemia (SA) is also due to malaria (Gendrel *et al*., 1992; Diop *et al*., 1997).

While, it is agreed that mortality and morbidity is increased in the homozygous SCD, when they are infected with malaria, there is ample evidence that the S trait accounts for the increased survival of children in early life in malaria endemic areas (Fleming *et al*., 1979; Serjeant and Sergeant, 2001; Kennedy, 2002).

Rationale for a review: Malaria accounts for significant mortality and morbidity due to various crises among SCD who comprise about 2.5% of the population in West Africa. Severe anaemia precipitated by malaria results in blood transfusions and since SCD and malaria occur mostly in parts of the world where HIV prevalence is high and blood screening procedures suboptimal, the risk of transmission of HIV is high and has been documented (Fleming, 1988; Hellenberg *et al*., 2005).

Hospitalizations/caring for SCD lead to great economic, physical and emotional costs on the family, while school absenteeism and poor progress in school constitute serious problems among affected children (Akinyanju, 1989; Ohaeri and Shokunbi, 2002).

Another reason is that pain relief is mostly inadequate for this patients and immense suffering that accompanies the VOC which can also lead to death (Schnog *et al*., 1998; Westerman *et al*., 1997). By preventing precipitating factors like malaria this can be reduced.

The last main consideration is that of the huge cost to the patient, family and health service in terms of hospitalization, repeated outpatient visits, blood transfusions and morbidity could be averted with optimum prevention. Such resources could be channeled to other productive ventures considering the great economic constraints in most places where this disorder occurs. Long term benefits of malaria prevention in SCD would be improved growth and development of such individuals.

There is agreement about protecting vulnerable groups from malaria and the optimum way of achieving this aim in SCD is the subject of this review.

METHODS FOR MALARIA PREVENTION

Malaria is a complex disease and its epidemiology varies in different parts of the world and requires different approaches for prevention and control in different places. In the following paragraphs, the various approaches available are reviewed.

Chemoprophylaxis: Evidence has accumulated over the years from trials on the efficacy and effectiveness of chemoprophylaxis against malaria. A recent Cochrane review of 19 randomized trials that were all conducted in

Africa including Nigeria showed that prophylaxis and intermittent treatment significantly reduced clinical malaria attacks, severe anaemia and admissions to hospital and parasite and spleen rates (Meremikwu *et al*., 2005). There was inconclusive evidence on the effect of the measure on mortality from this review although another review suggests that chemoprophylaxis does have significant effect on mortality (Paul *et al*., 2003). Two of the trials reviewed showed no evidence for delayed development of natural immunity and neither is the fear of rebound mortality and morbidity after stopping prophylaxis been substantiated. It was suggested that long term studies with larger samples could be conducted to better confirm this (Meremikwu *et al*., 2005; Paul *et al*., 2003; Greenwood *et al*., 1995, 2004). Various drugs have been used for prophylaxis in children including chloroquine, pyrimethamine plus dapsone (Maloprim$^{R)}$) and proguanil. These drugs are relatively safe and cost-effective.

Although, studies have claimed the effectiveness of chemoprophylaxis in reducing deaths, painful crises and hospital admissions among SCD individuals and had led experts to recommend the use of life long prophylaxis for this group of patients, there is little evidence to support this practice (Oniyangi *et al*., 2003). The use of proguanil is very popular in Nigeria and it is usually recommended for lifelong use. To date to the best of my knowledge, there has been no randomized clinical trial that has been conducted on the specific topic in Africa.

Lifelong drug use offers several challenges which include low compliance, side effects and unaffordable cost of therapy, as well as fears about the development of drug resistant parasites when a drug is used for long term prevention and this is a potential drawback for this option (Meremikwu *et al*., 2005; Greenwood, 2005).

Intermittent Preventive Treatment (IPT): Another option for malaria prevention is the use of Intermittent Preventive Treatment (IPT) with Sulfadoxine/Pyrimethamine (SP) and possibly some other antimalarials like Lapdap and mefloquine. IPT involves the administration of a full course of an antimalarial at predefined intervals to a population at risk has been tried in pregnant women, infants and older children with success (Schellenberg *et al*., 2001, 2005; Massaga *et al*., 2003; White, 2005; Macete *et al*., 2005; Chandramohan *et al*., 2005; Cisse *et al*., 2006; Dicko *et al*., 2004). Even though the mechanism of the protective effect of IPT is not very clear, it is thought to be either through prophylaxis or intermittent treatment (White, 2005; Schellenberg *et al*., 2005). IPT for infants (IPTi) given at the times of routine immunizations at 2, 3 and 9 months of life have been found to reduce the incidence of malaria and anaemia in Tanzania, Ghana and Mozambique. Studies of seasonal IPT use in areas, where malaria transmission is highly seasonal and affects older children has shown good results from Senegal and Mali (Schellenberg *et al*., 2005; Cisse *et al*., 2006).

Intermittent preventive treatment therefore offers another possibility in SCD. It eliminates the need for daily use of drugs and may offer opportunities for observed treatment at clinic visits thereby reducing non compliance. The occurrence of side effects will also be less likely compared to daily use of drugs.

Drugs best for IPT, their side-effects, dose and dosing regimen, effects of IPT on the development of functional immunity in children as well as methods of delivery of IPT to the target population such as during routine immunization or at school or during clinic visits are important questions for research researched.

Insecticide Treated bed Nets (ITNs): Insecticide treated bed nets (ITNs) have been studied in various groups of people and have been found to be effective in many parts including West Africa (Lengeler, 2004). Five randomised trials provided strong evidence that ITNs can reduce overall mortality in children by 20%. This review also provided a strong evidence for the impact on child health with a 50% reduction in the number of uncomplicated illnesses due to malaria among ITN users compared to those who did not use net and a 39% reduction for those who used untreated nets. ITNs also reduced parasite prevalence by as much as 13% and the use of treated nets resulted in an increase in the mean haemoglobin concentration among children, reduced cases of severe anaemia and other forms of severe malaria as well as an overall reduction in child mortality and morbidity especially in the first 3 years of life. Apart from personal protection wide use of ITN in a community can provide some herd effect and protect some that are not ITN users (Lengeler, 2004; Shiff, 2002).

The Global Malaria Partnership (GMP), through collaboration with several partners is helping countries to provide ITNs with subsidies from donors. The Abuja summit in 2000 saw African leaders pledging to provide ITNs to 60% of the children and pregnant women in their countries by 2005. Such target remains to be met at the end of the year 2005 in Nigeria where the culture of net use is not new but ITNs have been slow in coming. Studies have shown that many people in Nigeria are willing to pay for the ITNs when they are aware of its benefits but this is constrained by socioeconomic status (Onwujekwe and Uzochukwu, 2004; Goodman *et al*., 1999).

Despite the efficacy and cost-effectiveness of ITNs the main challenges are to reach the poorest and

peripheral parts of Africa as well as determining how best to finance sustainable programmes for the region (Goodman *et al*., 1999). Some studies on social marketing and public-private partnership offer some hope in this direction (Armstrong *et al*., 2001 Schellenberg *et al*., 2001; Kikumbih *et al*., 2004).

Other challenges to the ITN programmes are low re-impregnation rates, resistance to insecticides by mosquitoes and possible delayed development of functional immunity. Recent advances have made effective long lasting bed nets (LLN) available and these nets can last throughout their life span of about 3 years. The use of mixtures or mosaics of insecticides to delay the emergence of resistance in mosquitoes as well as the development of new ones are research priorities (Lengeler, 2004; Shiff, 2002; Aikins *et al*., 1998).

Concerning functional immunity a recent study looked at high, moderate and low areas of transmission with respect to the age of cerebral malaria, severe anaemia and other forms of malaria. The study found an increasing median age of severe disease with decreasing transmission intensity. However, severe anaemia occurred more commonly in those less than 2 years of age irrespective of the transmission intensity. Cerebral malaria was low in areas of high transmission intensity compared to areas of moderate and low intensity for all age groups studied (Reyburn *et al*., 2005). This tends to suggest that case-fatality from cerebral malaria may increase if transmission is prevented by the use of ITNs but further research is need in order to answer this question.

As Nigeria makes efforts to make ITNs universally available, it is important to recognise the high risk that malaria poses to SCD and specifically target the population for coverage. As earlier discussed delivery methods will have to be innovative and make use of all resources that can be mobilized both in the private and public sectors.

Malaria vaccines: In the last decade there have been renewed efforts at vaccine development due to private-public partnerships which have brought together essential human and financial resources for such a demanding and challenging venture as malaria vaccine research (Ballou *et al*., 2004; Greenwood *et al*., 2005; Shiff, 2002). Researchers have found difficulty in identifying which of the many antigens of the parasite serve critical function to the parasite and should therefore be selected for the vaccine development.

The pre-erythrocytic (mainly circumsporozoite antigen), asexual stage, transmission blocking and multicomponent vaccines are all being investigated. The most promising candidate is RTS, S/AS02, a pre-erythrocytic vaccine, which has shown substantial but short-lived protection in volunteers. In a trial in Mozambique, the vaccine provided 30% protection against the first episode of malaria and 58% protection against severe malaria among children. However, the development of a vaccine requires sustained human and financial commitment for its success and its place in SCD management will have to be carefully evaluated though it offers hope.

Malaria vaccines will eliminate the problems associated with drug use such as lack of compliance and financial difficulties. Achieving adequate coverage of the target population will be a key determinant of the success of its use when available and provision of the vaccine can be integrated into the maternal, newborn and child health programmes in Nigeria and elsewhere.

Other methods used in malaria control: These include environmental manipulation, Indoor Residual Spraying (IRS), zooprophylaxis and use of larvivorous fish to control vectors. The applications of control measures in a setting require the knowledge of vector biology and behaviour, socioeconomic level of the people as well as human behaviour (Shiff, 2002; Greenwood *et al*., 2005). This control measures if effectively deployed will be of benefit to the whole population SCD patients inclusive.

Integrated malaria control aims to ensure that those who do get infected are promptly treated at the same time controlling the transmission of the parasite by effective vector control and environmental manipulation and also by offering personal protection. The broadest spectrum is an eradication plan which will require the effective deployment of all available tools.

CONCLUSION

Despite the newness of IPT it is an attractive option for SCDs because intermittent use could lead to less cost and better compliance when compared to the current practice of daily drug use being practiced in Nigeria. Delivery of the IPT can be studied in different situations to see which is best either at clinic visits, by health workers at home or by parents. ITNs have proven benefits and a feasible method in SCD as in all others who are predisposed to attacks of malaria. Its use eliminates drug use and side effects, but needs to be used appropriately and consistently for best results. Perhaps what SCDs need is a combination of approaches for best results. Because of the fact that appropriate and consistent use of ITNs may not be possible all the time, combining this approach with IPT requires dedicated research. The need for a research into the subject is urgent in Nigeria, where a large population of SCD patients reside and encounter the hazards of malaria on a daily basis.

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