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Mini Review

Zinc Supplementation to Combat Infections in Children with Sickle Cell Anemia

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ABSTRACT

Sickle Cell Anemia (SCA) is a global genetic disorder, prevalent primarily in Sub-Saharan Africa, where it significantly contributes to childhood mortality. Infections are a major threat to individuals with SCA, emphasizing the urgent need for effective preventive strategies. Zinc deficiency, prevalent in SCA patients, compromises immune function, making them susceptible to infections. While zinc supplementation has shown promise in older individuals, its efficacy in children under five with SCA remains unexplored. This study addresses a critical knowledge gap in preventing infections in young children with SCA, with the potential to transform clinical practice, save lives, and improve the health of affected children, not only in Uganda but also in other regions heavily affected by this disease.

Keywords: Sickle cell anemia; Zinc supplementation; Infection prevention; Children; Randomized clinical trial; Sub-Saharan Africa.

INTRODUCTION

Sickle Cell Anemia (SCA) is a widespread genetic disorder, recognized as the most prevalent inherited hemoglobinopathy worldwide [1]. This condition primarily affects red blood cells, causing them to take on a characteristic sickle shape, leading to various complications. One of the most pressing concerns for individuals with SCA is their susceptibility to infections, a major contributor to illness and mortality, particularly among children in Sub-Saharan Africa, where the disease is highly prevalent.

In Sub-Saharan Africa, it is distressing to note that a staggering 50%-90% of children with SCA don't survive beyond their fifth birthday [2], with infections playing a pivotal role in this grim statistic. Consequently, there is an urgent need for effective interventions to reduce the incidence and severity of infections in this vulnerable population [3].

One promising avenue of research has shed light on the critical role of zinc in the health of individuals with SCA. A significant proportion of both adults and children afflicted with SCA suffer from zinc deficiency, which has a detrimental impact on their immune system, rendering them more susceptible to infections [4-8]. Zinc is a vital mineral required for various immune functions, including the development and function of immune cells.

Recent studies have explored the potential benefits of zinc supplementation in individuals with SCA. These investigations have yielded encouraging results, particularly in adolescents and adults. Zinc supplementation has been shown to enhance immune function, reduce the risk of infections, and improve overall health outcomes in these age groups.

However, an important gap in our knowledge remains. Despite the promising findings in older individuals, there is currently a lack of data regarding the effectiveness of zinc supplementation for preventing infections in children under the age of five who have SCA [9]. This is a critical area of research that needs to be addressed promptly to ensure that young children with SCA receive the best possible care and protection against infections.

To fill this knowledge gap, researchers are actively pursuing studies specifically focused on young children with SCA. These investigations aim to determine whether zinc supplementation can be a valuable strategy for reducing the incidence and severity

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of infections in this vulnerable age group. The hope is that by addressing this question, we can develop evidence-based recommendations and interventions that will improve the quality of life and life expectancy of children living with SCA in Sub-Saharan Africa and around the world [10].

Sickle cell anemia remains a significant health challenge globally, particularly in Sub-Saharan Africa, where children face a high risk of infections and premature death. Zinc deficiency, which is common in individuals with SCA, exacerbates this risk. While zinc supplementation has shown promise in older individuals, more research is needed to establish its effectiveness in preventing infections in children under the age of five with SCA. Bridging this knowledge gap is crucial to developing targeted interventions that can save lives and improve the health of children living with SCA in high risk regions.

LITERATURE REVIEW

The study represents a significant step towards addressing the critical knowledge gap surrounding the use of zinc supplementation as a potential intervention to reduce the burden of infections in young children with Sickle Cell Anemia (SCA). This review is designed as a randomized, placebo controlled, double blind clinical trial, a gold standard in scientific inquiry, aimed at providing robust evidence on the effectiveness of zinc supplementation. The trial will focus on a cohort of 250 Ugandan children aged between 1.00 and 4.99 years who have been diagnosed with SCA.

The choice of Uganda as the study location is not arbitrary; rather, it reflects the high prevalence of SCA in Sub-Saharan Africa and, in particular, the significant impact of the disease on children in this region. Uganda, like many Sub-Saharan African countries, grapples with a disproportionately high mortality rate among young children with SCA due to the increased susceptibility to infections. The prevalence of SCA is notably high in this region, making it an ideal setting for research aimed at improving the health and wellbeing of affected children.

The study design incorporates several key features that enhance its scientific rigor and reliability. First and foremost, it will be randomized, meaning that participants will be allocated to either the zinc supplementation group or the placebo group entirely by chance. This minimizes bias in the selection of participants and ensures that the groups are comparable at the outset, allowing for valid comparisons between the two. Furthermore, the trial is placebo controlled, meaning that a group of participants will receive a placebo, which is an inactive substance that looks identical to the zinc supplement. This control group is essential to determine whether the observed effects are indeed due to the zinc supplementation and not attributable to other factors. It helps researchers establish a baseline against which they can measure the effectiveness of the intervention.

The study is also double blind, ensuring that neither the participants nor the researchers are aware of who is receiving the active treatment (zinc) and who is receiving the placebo. Double blinding is a critical aspect of the trial, as it eliminates potential biases that can arise from the participants' or researchers' knowledge of group assignments [11]. This feature enhances the study's credibility and reduces the risk of unintentional influences on the outcomes.

The intervention itself involves daily zinc supplementation, administered in the form of a 10 mg oral dispersible tablet. This dose has been carefully selected based on existing knowledge of zinc requirements and its safety profile in children of this age group. The choice of an oral dispersible tablet is particularly advantageous for young children, as it ensures ease of administration and compliance.

The study duration will span 12 months, providing a comprehensive assessment of the long term impact of zinc supplementation on infection rates and overall health outcomes in children with SCA. This extended observation period is crucial for capturing any potential delayed or cumulative effects of the intervention.

Throughout the study, rigorous data collection and analysis procedures will be employed. Various health indicators, including infection rates, hospitalization rates, and overall wellbeing, will be closely monitored and assessed [12]. This will enable researchers to draw robust conclusions about the effectiveness of zinc supplementation in reducing the burden of infections in young children with SCA.

In addition to evaluating the primary outcome, the study will also explore secondary outcomes, such as changes in zinc levels in the blood, potential adverse effects of supplementation, and markers of immune function. These secondary endpoints will provide valuable insights into the mechanisms by which zinc may exert its protective effects and help ensure the safety of the intervention.

This randomized, placebo controlled, double blind clinical trial in Uganda represents a pivotal endeavor to address the urgent need for evidence based interventions to improve the health and wellbeing of young children with sickle cell anemia [7,4]. By rigorously evaluating the impact of zinc supplementation over a 12-month period, this research aims to shed light on whether this intervention can reduce the incidence and severity of infections in this vulnerable population. Ultimately, the findings of this study have the potential to transform clinical practice and improve the quality of life and life expectancy of children with SCA not only in Uganda but also in other regions heavily affected by this disease.

DISCUSSION

The study aims to investigate the potential of zinc supplementation in reducing infections in young children with Sickle Cell Anemia (SCA). If significant reductions in infection rates are observed, future multicenter studies in less well-resourced clinics will be considered, possibly using a pre post intervention design [13]. A substantial decrease in infections with zinc supplementation could make further placebo controlled trials ethically questionable.

However, if the reduction in infection rates is more modest (e.g., a 20%-25% reduction), a larger placebo controlled, multi-center trial will be warranted to establish zinc efficacy definitively. Zinc

supplementation is cost-effective, has minimal side effects, and has been successfully used in children in Low and Middle Income Countries (LMICs) to prevent infections.

Potential limitations and alternatives have been considered. If infection rates are lower than expected, a protocol amendment to increase the sample size may be considered [14]. However, substantial decreases in infection rates are unlikely due to various factors, including the age group targeted, differences in hospital readmission rates, and the assessment of all infections, not just specific ones like malaria.

The chosen zinc dose of 10 mg/day is considered balanced between safety and efficacy and has been used effectively in children without SCA. Comparing different doses would require a much larger sample size. The use of plasma zinc levels as a surrogate for efficacy is not suitable, as earlier studies have shown efficacy without changes in levels [15].

Zinc supplementation is not standard care for children with SCA or healthy children in Uganda. National guidelines recommend 20 mg of zinc daily during diarrhea episodes. In this study, if a child experiences diarrhea, zinc or placebo treatment will be halted, and open label zinc (20 mg) will be administered following national guidelines.

The standard of care for infection prevention in Ugandan children under 5 with SCA includes vaccinations, penicillin prophylaxis, and prophylaxis against malaria and helminth infections. The study will provide any necessary vaccinations, medications, or supplements that children have not received.

Hydroxyurea, recommended by the Ugandan Ministry of Health, will be offered to eligible participants based on clinical judgment. Hydroxyurea use will not be an exclusion criterion, as there is no evidence that it affects infection risk [16]. It will be included as a covariate in analyses.

Clinical trial results often vary between adults and children, necessitating a randomized placebo controlled trial to determine the efficacy of zinc supplementation in young children with SCA [3,5]. Given the evidence of zinc deficiency in this population, along with zinc's safety and cost effectiveness, this study could transform the health of African children with SCA by providing vital data on the potential benefits of zinc supplementation.

CONCLUSION

In conclusion, sickle cell anemia presents a significant health challenge globally, particularly in Sub-Saharan Africa, where it disproportionately affects children, contributing to high mortality rates. Infections are a major threat to children with SCA, emphasizing the urgent need for effective preventive strategies. Zinc deficiency, prevalent in this population, compromises immune function, making them more susceptible to infections. While prior studies have shown promising results in older individuals, a critical knowledge gap exists regarding the effectiveness of zinc supplementation in children under five with SCA. This study, a rigorously designed randomized, placebo controlled, double blind clinical trial conducted in Uganda, aims to address this gap. By evaluating the impact of zinc supplementation over a 12-month period in young children with SCA, this research could transform clinical practice and improve the quality of life for affected children not only in Uganda but also in regions heavily affected by this disease. It represents a vital step toward providing evidence based interventions to save lives and enhance the health of this vulnerable population.

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