The Efficacy and Safety of Levamisole in African Children With Idiopathic Nephrotic Syndrome: A Protocol for Systematic Review and Meta-Analysis

Christie Divine Akwaowo
University of Uyo Teaching Hospital
Emmanuel Okechukwu Nna (e.nna@themping.org)
Biosystem Laboratories https://orcid.org/0000-0001-6791-2336
Henrietta Uchenna Okafor
UNTH: University of Nigeria Teaching Hospital
Adanze Onyenonachi Asinobi
University of Ibadan College of Medicine
Ann Ebele Aronu
University of Nigeria Teaching Hospital
Olubukola Adeponle Adesina
University College Ibadan
Vivian Ololade Akanni
University of Essex
Datonye Christopher Briggs
College of Medical Sciences Teaching Hospital
Francis Chinedu Ugoeze
Federal Medical Center
Ufuoma Aduh
WHO ASABA
Haruna Usman Liman
College of Medical Sciences
Ifeoma Joy Okoye
University of Nigeria Teaching Hospital
Richard Chinaza Ikeagwulonu
ALEX EKWUEME Federal Teaching Hospital Abakaliki

Protocol

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Abstract

Background

Nephrotic syndrome (NS) is one of the most common childhood renal disorders globally, with an incidence of 2 to 7 cases per 100,000 children. A characteristic feature is massive proteinuria which may rapidly progress to end stage kidney failure, if uncontrolled. Most of the cases in children are steroid sensitive but associated with frequent relapses. Levamisole, a cheap antihelminthic has been used as steroid sparing agent in steroid sensitive NS (SSNS). This study assesses the efficacy and safety of Levamisole in African children with idiopathic nephrotic syndrome.

Methods

We will conduct a systematic review and meta-analysis of all Randomised controlled trials which reported African children with Idiopathic nephrotic syndrome who were on Levamisole compared to other drugs. Ten databases including PubMed, African Journals Online, Google Scholar, Cumulative Index to Nursing and Allied Health Literature, EMBASE, Cochrane Library, Web of Science, Scopus, Clinicaltrial.gov and Research Gate will be searched using a search strategy. The search will have no time restrictions, but studies must have been conducted among African children residing in Africa and are retrievable in the English Language. Studies will be selected based on inclusion and exclusion criteria by two independent reviewers without blinding. The study quality will be assessed using the Pedro scale and risk of bias evaluated using the Cochrane Risk of Bias tool. Eligible screened studies will be inlcuded for meta-analysis using the CMA Software. Statistical, clinical and methodological heterogeneity will be tested. Subgroup analyses and meta-regression will be performed on rate of relapses, adverse event and drug dose.

Discussion

The primary outcome will be the proportion of children with remissions and or relapses within 6 -12 months post initiation of levamisole or comparators with effect size being the relative risk. Safety of Levamisole will be measured using reported adverse events. Moderating effects of age, gender, duration of illness, and dosage of Levamisole on the duration of remission, frequency of relapses and adverse events will be examined.

Systematic Review Registration

This protocol has been registered in PROSPERO, with registration number CRD42020213327.

Background

Nephrotic syndrome (NS) is one of the most common childhood renal disorders requiring paediatric nephrologist consultation, globally. It has a characteristic feature of massive proteinuria which, if uncontrolled may cause rapid progression to end stage kidney failure. Childhood nephrotic syndrome has

a reported incidence of 2 to 7 cases per 100,000 children and a prevalence of nearly 16 cases per 100,000. [1,2] In Tropical Africa, NS is an important cause of chronic kidney disease (CKD) [3-6] and the incidence of NS as a cause of childhood CKD may be as high as 45% [4] but the exact prevalence of childhood nephrotic syndrome in this region is not known. Olowu *et al* [7] in a comprehensive comparative review on childhood NS found that among the 45 African countries in Tropical Africa, only 11 countries, representing 53.9% of the population of the region, have information on the burden of childhood NS indicating substantial underreporting.

Glucocorticoids have remained the mainstay of treatment for NS since their introduction in the 1950s,[8,9] and steroid responsiveness is regarded as its most important prognostic indicator.[1] Childhood idiopathic nephrotic syndrome often responds to steroids but runs a course characterized by relapses and remissions exposing the patients to the adverse cumulative effects of steroids.[10] Globally, a lot of regional practice variations exist in the treatment of nephrotic syndrome and even in the same country variations occur as demonstrated in a study from Nigeria recently.[11] In the early 1970s, the International Study of Kidney Disease in Children (ISKDC) recommended daily oral steroid 60 mg/m2 for 4 weeks followed by 40 mg /m2 on alternate day for 4 weeks [10]. Subsequently, the use of high dose steroid (60mg/ m^2 /day) for 6 weeks followed by 40 mg/m2 on alternate day for 6 weeks showed reduction in frequency of relapses and steroid dependency [12]. Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (2012) also suggested that same dose with more flexibility of using oral prednisolone (OP) 60 mg/m2 /day for 4–6 weeks followed by tapering over 2–5 months [13]. The prolonged tapering over 6-7 months was based on Cochrane reviews in the 1990s which suggested that the longer steroid therapy was associated with less frequent relapses.[14] However, more recent randomized controlled trials have shown that short course (2–3 months) treatment with OP is neither inferior to long course (4–6 months) nor associated with increased risk of frequent relapses and steroid dependency [15-18]. Most recently the Human Hereditary and Health in Africa-Kidney Disease Research Network (H3A-KDRN), generated a consensus statement on the management of childhood NS in sub-Saharan Africa using the modified Delphi approach to limit the observed variability in the management of childhood NS in Africa.[19]

Among Caucasian children with NS, more than 85–90% of children are initially steroid sensitive and achieve remission within 4–6 weeks and 10–15% are initially steroid resistant (SR) [10, 13, 18]. The picture in Tropical Africa was characterized by paucity of MCD and steroid resistance in the 1960s to 1980s but recent reports are pointing to increasing steroid responsiveness in Sub-Saharan Africa as a whole [7, 20-26]). About 60–80% of steroid responders develop relapses and 40–60% will become frequent relapsers (FR) and 30% become steroid dependent (SD). Patients with FR, SD and SR are known as difficult nephrotic syndrome (DNS) since these require alternate immunosuppressive strategies to avoid steroid toxicity, severe infections, hypertension and acute kidney injury or chronic kidney disease (CKD). Treatment strategies utilised in the management of FR and SD nephrotic patients have included repeat courses of prednisone to achieve remission of recurrent episodes and/or the addition of other immunosuppressive medications, such as Calceneurin inhibitors, mycophenolate mofetil, alkylating agents; Levamisole an immunomodulatory agent for FR patients and in recent times Rituximab, to reduce

the number of relapses and prevent major side effects of steroid treatment [27,28]. The prevalence of frequent relapses, steroid dependence and secondary resistance is scarcely reported from our region but seen in clinical practice.

Levamisole, a cheap and relatively safe antihelminthic agent is one of the several alternative medications found useful as steroid sparing agents in steroid sensitive NS (SSNS), they prolong periods of remission. [29,30] In low- and middle-income countries in Africa where patients may not afford the expensive alternative immunosuppressive agents this drug may be a useful alternative. [19,31] It is known that there are disparities in the epidemiology and response to treatment in various clinical conditions [32], it is therefore necessary to evaluate the efficacy of the drug in Africa and if found efficacious, it will improve access to appropriate management and quality of life of these patients.

A few key terminologies are explained. Nephrotic Syndrome (NS) is characterized by massive clinical edema, nephrotic range proteinuria (spot urine protein creatinine ratio (suPCR) ≥2 or 3+ protein on dipstick), hypoproteinemia (< 5.5 g/dl), hypoalbuminemia (< 2.5 g/dl); with or without hypercholesterolemia (> 250 mg/dl). Frequent Relapse (FR) is two or more relapses in 6 months or more than 4 in a 12 months period. Steroid Dependent Nephrotic Syndrome (SDNS) is two consecutive relapses on steroid therapy or occurred within 14 days of switching to alternate day prednisolone or as prednisolone is being tapered. Steroid Resistant Nephrotic Syndrome (SRNS) is persistence of edema and or proteinuria (suPCR > 2) after 4–6 weeks of oral prednisolone (OP) 60 mg /m2 / day. Complete remission (CR) is disappearance of edema and proteinuria (suPCR < 0.2)/urine dipstick nil or < 1+. Partial remission (PR) is disappearance of edema but persistence of non-nephrotic range proteinuria (suPCR 0.2-< 2). Difficult nephrotic syndrome (DNS) is frequent relapsing, SDNS and SRNS, were considered as DNS. Cyclophosphamide (CPM) resistant NS is persistent nephrotic range proteinuria and edema after 8–12 weeks of 2-3 mg/kg/day of CPM.

Cyclosporine (CS) resistant NS is persistent nephrotic range proteinuria and edema after 6 months of 5 mg/kg/day of cyclosporine.

Methods/ Design

Aim: The overall aim of this study is to assess the efficacy and safety of Levamisole in African children with idiopathic nephrotic syndrome.

Study objectives:

1. to determine the proportion of children on Levamisole who sustain remission more than 6 months post initiation.
2. to determine the proportion of children on Levamisole with more than 2 relapses within 6 months.
3. to compare remission and relapse rates between patients on Levamisole and those on other immunosuppressive drugs,

4. to determine the proportion of children with idiopatic nephrotic syndrome on Levamisole who sustained remission within 6 months.
5. Sub-group analysis of effect of gender and duration of illness on duration of remission and frequency of relapses.
6. Subgroup analysis that will include:

    a. Children with frequent relapses
    b. Children who are steroid dependent
    c. Children resistant to steroid treatment

7. Meta-regression of age and dosage of Levamisole on duration of remission and frequency of relapses.

Design: A systematic review and meta-analysis will be conducted on screened and eligible clinical trials, randomized control trials, and quasi-randomized studies done on African children living in Africa who have idiopathic nephrotic syndrome and have been treated with levamisole. The study will cover all available data from 1969 (when levamisole was first commercially manufactured) to date 2020.

Inclusion criteria are:

a. Interventional studies including clinical trials, randomized control trials and quasi-randomized studies,
b. study must be conducted on African children,
c. studies must have Levamisole as drug for comparison,
d. studies must have remission and / or relapse rate as measurable outcome,
e. studies must be published or retrievable in the English language and
f. studies must be available in electronic databases.

Exclusion criteria are:

a. All narrative studies, including letters to editors, reviews, commentaries and editorials,
b. All non-interventional studies including observational studies,
c. All interventional studies not done in Africa,
d. Duplicates of same studies,
e. Studies with no measurable outcomes and
f. Studies that are not retrievable in the English language

This review will be reported in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2015 Statement).

Study Characteristics:

Research Questions: The following review questions will be addressed:

a. Does levamisole sustain remission for 6-12 months in African children with Idiopathic Nephrotic syndrome?
b. Is the rate of relapse reduced within 6-12 months in African children with Idiopathic Nephrotic Syndrome treated with levamisole?
c. Is levamisole at a clinical dose of 2.5 mg per kg per day safe in African children with Idiopathic Nephrotic Syndrome?
d. Do age, gender, duration of illness, and the dose of levamisole moderate the duration of remission and frequency of relapses in African children with Idiopathic Nephrotic Syndrome?

The PICOS is as follows

Participants: African children below 18 years, already diagnosed with idiopathic nephrotic syndrome and have received steroid treatment.

Intervention: Treatment with Levamisole.

Comparator: Treatment with steroids: prednisolone or other immunosuppressive agents: cyclosporine, cyclophosphamide, Mycophenolate mofetil, Rituximab, Tacrolimus and Chlorambucil

Outcomes: a: proportion of children on levamisole with remission within 6 months post initiation, b) proportion of children on other immunosuppressants with remission within 6 months post initiation, c) proportion of children on levamisole with relapses within 6 months post initiation, d) proportion of children on other immunosuppressants with relapses within 6 months post initiation, e) proportion of children on levamisole with sustained remission beyond 6 months post initiation; f) proportion of children on levamisole without remission within 6 months post initiation and g) number of adverse events in children treated with levamisole.

Effect Size: Relative Risk (RR). Other comparable effect sizes in very similar study designs will be converted to RR using the Comprehensive Meta-analysis Software CMA version 3 (BioStat, USA).

Information sources

The search will employ sensitive topic-based strategies designed for each database. The following databases will be searched: PubMed, AJOL, Google Scholar, CINAHL, EMBASE, Cochrane Library, Web of Science, Scopus, ClinicalTrials.gov and Research Gate. Only randomized control trials and clinical trials retrievable in English language will be included. The time frame is 1969 to 2020.

Search strategy

The search strategy will include MeSH terms, text words, and entry terms. The search strategies to be used in the databases are shown in Table 1:

Data Extraction

Studies will be searched using the search strategy. There are four levels of data screening in this study: a) level 1 is based on study design: only randomized clinical trials and clinical trials conducted in Africa will be extracted from the literature. All observational studies and comments will be excluded; b) level 2: selected studies will first be screened by titles and abstracts using entry terms, keywords, and meSh terms;c) level 3: selected studies will be further screened by full-text reading using the same strategy; d) level 4: snowballing of literature from included studies.

Thirteen reviewers are involved in this study. A pair of reviewers will independently screen studies from each database. Conflicts will be resolved by a third independent reviewer. The review is without blinding. All searched, screened, and retrieved items will be exported to the bibliographic software, Endnote version 9. After screening, data will be exported to Microsoft Excel. All relevant studies that meet the inclusion criteria and are exported to Microsoft Excel will also have full texts retrieved and read to enable snowballing search on references. Authors of eligible articles with missing data will be contacted via email address and telephone.

b. Selection process:

Two independent reviewers will screen full texts of all eligible RCTs, and control trials identified from our databases and snowballed articles and conflicts will be resolved by a third researcher on the team to confirm whether each study meets our eligibility criteria.

c. Data collection process

De-duplication of the studies will then be done in the EndNote version 9. Eligible studies will be exported into Microsoft Excel. The following data will be extracted from each study: a) First author's surname and year of publication, b) effect size (RR, measuring remission rate and relapse rate within 6 months post initiation; no remission beyond 6 months post initiation), c) sample size, d) mean age, e) gender, f) the dose of Levamisole, g) duration of illness, h) frequency of relapses and i) number of adverse events

Data from Excel will be exported to CMA Software for meta-analysis.

Risk of bias

The Cochrane Risk of Bias tool which considers sequence generation, allocation concealment, and blinding and other aspects of bias will be used to assess the study risk of bias. The overall rating of risk of bias for each study will be the lowest rating for any of the criteria (e.g. if any domain is scored high risk of bias, the study will be considered high risk of bias). Any discrepancies between reviewers for any of the above steps will be discussed by the reviewers until consensus is achieved. Pedro scale of quality scoring will also be applied.

We will also contact authors of primary publications, collaborators and/or sponsors of clinical trials for missing outcome data or unclear information.

1. Reporting of study: whether remission rate or relapse rate/relapse reduction rate as reported will be done at the outcome level and effect sizes converted for uniformity eventually.
2. Heterogeneity will be assessed at the study level using Q statistic and its p value, I^2 and Tau squared.
3. Publication bias will be assessed at the study level using funnel plot.
4. Statement of study location will be done.

Data synthesis

a. Studies that passed the methodological quality assessment using the Cochrane Risk of Bias tool will be included for data synthesis. The results will be presented in tabular format in addition to a narrative synthesis.
b. The following shall be included into the meta-analysis:

    i. Reported proportion of relapse or remission within 6-12 months of initiation of therapy and sample size by individual studies. The effect size is RR. This is the primary outcome measure. This variable must be present for a study to be included.
    ii. Reported sub-group analysis of moderating effects of age, gender, duration of illness and dosage of Levamisole on duration of remission and frequency of relapses. Effect sizes are for age (mean), gender (categorical), frequency of relapses (relative risk).
    iii. Subgroup analysis that will include:

        a. Children with frequent relapses (categorical)
        b. Children who are steroid dependent (categorical)
        c. Children resistant to steroid treatment (categorical)

c. Screened and eligible studies will be quantitatively analyzed using the CMA Software Version 3 (BioStat, USA). For each reported relapse or remission, standard error and variance for each specific eligible study will be calculated by the CMA software. Subgroup analysis will also be done. To test for heterogeneity Cochrane's Q value and its p value, I^2, τ^2 will be used. The effect size to be used is RR and 95% confidence Interval (CI, 95%). Publication bias will be assessed using a funnel plot. As a rule of thumb, I^2 values of less than 40% will be considered low heterogeneity while values > 40 but < 75 % will be considered moderate and values > 75% are high. Subgroups analysis will be done using treatment modalities as a categorical data and moderator.

Meta-regression will be done with dose, age and duration of illness. The pooled effect size (relative risk) and subgroups analysis will be reported in forest plots. Both random and fixed effect models will be assessed, and the appropriate model will be taken based on the forest plots. Publication bias in the

selection of studies will be tested using funnel plot (trim and fill method) and test for funnel plot asymmetry.

Discussion

Presentation and Reporting of Results

The study selection process will be summarised in a flow diagram according to the PRISMA 2015 Statement and PRISMA-P Checklist (attached). A table of search strategy in various databases showing text words, MeSH and entry terms will be included. List of included studies will be summarized in a table. Quantitative data such as relative risk, 95 % CI, P values, relative weights assigned to studies and heterogeneity tests will be included in the forest plots. A table of quality scores and risk of bias of each eligible study will be included. Forest plots to show sub-group analysis will be included. Regression plots on dose, age and duration of illness will be included in separate plots.

Using the various data, the efficacy of levamisole and its safety will be evaluated in comparison to other immunosuppressive drugs. It will also examine if efficacy of levamisole is dose and age dependent. It will evaluate if duration of illness prior to initation of levamisole therapy has impact on remission and relapse rates. This study will assess safety of levamisole in African children using data from adverse events.

Conclusions drawn from the review will be made available to Pediatricians and Nephrologists who manage African children with nephrotic syndrome and health authorities. The final study will finally be published in a peer-review journal and the findings will be submitted to relevant health authorities.

Abbreviations

AGCPN - Association of Good Clinical Practice of Nigeria

AJOL - African Journals Online

CINAHL – Cumulative Index to Nursing and Allied Health Literature

CKD – Chronic kidney disease

CR – Complete remission

DNS – Difficult Nephrotic Syndrome

FR – Frequent Relapsers

H3A-KDRN – Human Hereditary and Health in Africa-Kidney Disease Research Network

ISKDC – International Study of Kidney Disease in Children

KDIGO – Kidney Disease: Improving Global Outcomes

NS – Nephrotic syndrome

OP – Oral prednisolone

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SD – Steroid dependent

SR – Steroid resistant

SSNS – Steroid sensitive nephrotic syndrome

SDNS – Steroid dependent nephrotic syndrome

Declarations

1. Ethics approval and consent to participate: The systematic review methodology does not require ethical approval due to the nature of the study design. The results of the systematic review will be published in a peer-reviewed journal and will be publicly available
2. **Consent for publication**: All reviewers/investigators consented to publication.
3. **Availability of data and materials**: This is not applicable to this study.
4. **Competing interests**: The authors declare no competing interests.
5. **Funding:** Funding for the study will be provided by the Association for Good Clinical Practice in Nigeria AGCPN
6. **Authors' contributions**: HO, EN, IO and CA conceived the study, HO and AA will review PubMed and AJOL; RI, UA, DB and CA will review Google Scholar; AO and AA will review Cochrane, VA and HL will review ResearchGate and ClinicalTrials.Gov, FU and OA will review CINAHL and Embase, EN, UA and IO will review Web of Science and Scopus. Early Protocol drafted by HO and reviewed by EN and revised by all authors.
7. Acknowledgements: Profound gratitude to AGCPN for funding the study.
8. Authors' information (optional)
9. **Support:** The Association for Good Clinical Practice in Nigeria (AGCPN)
   AGCPN provided the platform and funding for the review
10. **Guarantor of the Review**: Dr Emmanuel Nna
11. **Conflict of Interest**: The authors declare none.

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Tables

Table 1: Search strategy

S/No	Database	Search strategy
1	PubMed	(((children) AND Levamisole) AND Nephrotic syndrome) AND Idiopathic nephrotic syndrome
2	AJOL	(children) AND Levamisole) AND Nephrotic syndrome) AND Idiopathic nephrotic syndrome AND AFRICA
3	Google Scholar	(children) AND Levamisole) AND Nephrotic syndrome) AND Idiopathic nephrotic syndrome AND AFRICA
4	Cochrane library	(children) AND Levamisole) AND Nephrotic syndrome) AND Idiopathic nephrotic syndrome
5	EMBASE	(((children) AND Levamisole) AND Nephrotic syndrome) AND Idiopathic nephrotic syndrome
6	Research Gate	(((children) AND Levamisole) AND Nephrotic syndrome) AND Idiopathic nephrotic syndrome
7	CINAHL	(((children) AND Levamisole) AND Nephrotic syndrome) AND Idiopathic nephrotic syndrome AND AFRICA
8	Web of Science	(children) AND Levamisole) AND Nephrotic syndrome)
9	Scopus	(((children) AND Levamisole) AND Nephrotic syndrome) AND Idiopathic nephrotic syndrome
10	ClinicalTrials.gov	(children) AND Levamisole) AND Nephrotic syndrome) AND Idiopathic nephrotic syndrome AND AFRICA

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