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A protocol for systematic review and meta-analysis on the burden of neonatal seizures in Nigeria

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Abstract: Neonatal seizures are a significant contributor to neonatal morbidity and mortality in Nigeria and the magnitude of the burden is unknown. A comprehensive systematic review is needed to determine the pooled magnitude and causes of neonatal seizures in Nigeria since the true estimate is yet to be determined. Therefore, this study aims to develop a protocol to assess the burden and causes of neonatal seizures in Nigeria.

A search strategy is developed using MeSH terms, text words, and entry terms. Nine databases will be searched including Pub-Med, African journals online, Google Scholar, Cumulative Index to Nursing and Allied Health Literature, EMBASE, Psych Info, Web of Science, Scopus, and Research Gate. Only observational studies, retrievable in the English language and conducted in Nigerian neonates will be included. The primary outcome of this study is the pooled prevalence of neonatal seizures in Nigeria. The secondary outcomes include the seizure types, causes, method of detection, and outcome in the neonates. Screening of identified studies will be done in End Note version 20 and duplicates re-moved, before exporting to Microsoft 365 excel sheet for data extraction by independent reviewers. Studies will be assessed for methodological, clinical, and statistical heterogeneity and if required, a meta-analysis will be done. Stata 16 IC will be used for data analysis. Various subgroup analyses will also be done. A funnel plot will be used for the assessment of publication bias. Results will be presented in tabular formats, narrative synthesis, and regression plots.

The data from this review will reveal the pooled prevalence of neonatal seizures in Nigeria. It will create an avenue for discussion on the types, causes, and outcome of neonatal seizures. The findings will also enable discussions on how to address the causes of neonatal seizures in Nigeria and provide evidence for policy recommendations to reduce morbidity and mortality resulting from neonatal seizures in Nigeria.

Trial registration number: This protocol is registered in PROSPERO with registration number CRD42020220097.

Keywords: Newborn, Prevalence, Incidence, Neonatal seizures, Seizures, Mortality, Nigeria.

Introduction

Neonatal seizures are a significant contributor to neonatal morbidity and mortality in Nigeria and the magnitude of the burden is unknown because healthcare facilities often lack the means to sufficiently diagnose, monitor, treat or even prognosticate neonates after neonatal seizures. Any seizure occurring within the first 28 days of life in the full-term infant or before 44 weeks of gesta-tional age in a preterm-infant defines neonatal seizure.[1] The risk for the occurrence of seizures in children is highest in the first month of life[2] since the immature state of the motor pathways in neonates makes them more susceptible to seizures.[3] A seizure represents the most characteristic manifestation of an underlying neurological compromise in the neonate and constitutes a neurological emergency requiring urgent diagnosis and management.[4] Therefore the presence of seizures in a

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neonate is a risk factor that increases the rates of long-term neurological sequelae and or death.[5] While neonatal seizures are clinically described as subtle, often inconspicuous, paroxysmal, repetitive, and stereotyped events,[3] they differ from those of older children and adults. The semiology noted in neonates who have seizures suggests onset is predominantly focal[6] and are classified according to the proposed 2018 International League Against Epilepsy (ILAE) task force group as clinical only, electro-clinical or electrographic only.[7]

Globally, the true incidence of neonatal seizures is unknown[8] due to considerable differences in reported incidences and prevalence, arising from varying methods used in identifying neonatal seizures and settings.[9] However, worldwide reported incidence of neonatal seizures in full-term neonates ranges from 1 – 5 per 1000 live births [8,10,11] in high-income and upper-middle countries. Studies reporting incidences from middle- and low-income countries are limited and two studies in Ethiopia and Kenya reported incidences of 13.6 per 1000 live births and 39.5 per 1000 live births respectively[12,13], suggesting a possibly higher incidence in these settings. Even among the preterm population, the reported incidence of neonatal seizures, based on clinical observation range from 3.9 – 57.5 per 1000 live births[10,14] in high-income countries and studies from middle and low-income countries are limited with two studies in Nigeria reporting incidences of 13.5 per 1000 live births and 47.6 per 1000 live births respectively[15,16] Other studies have reported incidence rates of neonatal seizure to range from 3.5 – 7.5 per 1000 live births[15,16] whereas other studies report prevalence ranging from 5 – 16.7 %.[17,18]

The causes of neonatal seizures are diverse and maybe unknown.[8,9]The different causes of seizures may co-exist in neonates, hence making definite aetiology problematic.[19] In the full-term neonates, hypoxic-ischaemic encephalopathy (HIE), CNS infections, and stroke are reported as the commoner causes while intravascular haemorrhage is the commonest cause in preterm neonates in higher-income countries.[19,20] Studies from different low and middle-income countries demonstrate that hypoxic-ischaemic encephalopathy (HIE), hypoglycaemia, hypocalcaemia, and CNS infections are the commoner causes of neonatal seizures.[8,12,17,21] However, intracranial haemorrhage, congenital malformations and genetic disorders of amino and organic acid metabolism are rarely documented[21] which may be due to variations in diagnostic techniques and obstetric care.

The onset of neonatal seizures occurs usually within the first week of life with about 37.5 – 80% occurring within the first 24 – 48 hours.[12,22,23] Onset usually depends on the cause and usually occurs later in preterm neonates when compared to term neonates.[19] Seizure types are generally classified into five – subtle, focal clonic and multifocal clonic, myoclonic, and tonic based on the seizure semiology according to Volpe.[24] The usual duration of seizures ranges between 10 – 120 secs

and is repetitive with a median of 8 minutes between each seizure episode.[22]

Most seizures in neonates occur without obvious clinical signs[25] and need diagnostic tools for continuous monitoring to properly arrive at a diagnosis that will help identify aetiology and also allow effective care and prognosis.[26] Unlike in high-income countries where the availability of diagnostic tools such as electroencephalography (EEG), video-EEG monitoring, and early neuro-imaging is complemented by clinical observation to make the diagnosis of neonatal seizures more accurate,[6] these facilities are not readily available in the middle and low - income countries like Nigeria where the diagnosis is mainly based on clinical observation.[12,21,27]

These differences can result in either over or under-estimation of the true incidence of neonatal seizures as a cause of long-term neurological morbidity and mortality. Not all neonatal seizures result in neurological deficits as 25 – 45% have a normal outcome.[14] However, about 25 – 31 % develop cerebral palsy,[14,28,29] 18 – 35 % epilepsy,[14,29] 19 – 27% intellectual disabilities[29] and 28 – 50% have developmental delays.[30] Prognosis of neonatal seizures ultimately depends on the primary cause of the seizures. Deaths from neonatal seizures have been reported among neonates from high, middle- and low-income countries and range from 7 - 16%.[12,14,29,31]

Although neonatal seizures are a common problem faced by neonates admitted into specialized health care facilities in Nigeria, diagnosis is mainly based on clinical observation.[16–18,21] With the proliferation of studies in Nigeria reporting neonatal seizures as a contributor to neonatal morbidity and mortality, a comprehensive systematic review is needed to determine the pooled magnitude of neonatal seizures in Nigeria since the true estimate is yet to be determined. This protocol is designed to enable a reliable review and meta-analysis, aimed at synthesizing the existing data and describing the burden of neonatal seizures in Nigeria.

The findings from this research will increase the understanding of the burden of neonatal seizures and provide evidence for policy recommendations to reduce neonatal mortality resulting from neonatal seizures in Nigeria.

Methods and Designs

The main objective of this study is to determine the burden and causes of neonatal seizures in Nigeria.

Specific objectives

- To determine the pooled prevalence of neonatal seizures in Nigeria
- To determine the pooled prevalence of neonatal seizures in preterm (gestational age<37 completed weeks) and term neonates (gestational age> 37 completed weeks).
- To determine the types and causes of seizures in

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preterm and term neonates.

- To identify the method of seizure detection in preterm and term neonates
- To summarize the outcome of seizure in preterm and term neonates.

Review questions

- What is the pooled prevalence of neonatal seizures in Nigeria?
- What is the pooled prevalence of neonatal seizures in preterm and term neonates?
- What are the types and causes of seizures in preterm and term neonates?
- What is the commonest method of seizure detection in preterm and term neonates?
- What is the outcome of seizure in preterm and term neonates?

Study design

This is a protocol for systematic review and meta-analysis of observational studies on neonatal seizures conducted in Nigeria. It includes cohort, cross-sectional, case-control, retrospective, and historical cohort studies. Other study designs are excluded including interventional studies. There is no time restriction for selecting primary studies.

Inclusion criteria

- Observational studies (cohort, cross-sectional, case-control, retrospective, and historical cohort studies)
- Studies of all years that are published or retrievable in the English language
- Studies that are available in electronic databases
- The study must be conducted in Nigerian neonates.
- The study must report the prevalence/incidence of neonatal seizures

Exclusion criteria

- All narrative studies, including letters to editors, reviews, commentaries, and editorials
- All interventional studies
- Studies not carried out in Nigeria
- Studies dealing with any other population outside neonates
- Duplicates of same studies
- Studies that are not retrievable in the English language
- Grey literature

The Picos is as follows:

Participants: all Nigerian neonates diagnosed with neonatal seizures
Exposure: not applicable
Comparator: not applicable
Outcome: The primary outcome of this study is the

prevalence of neonatal seizures in Nigeria. The measurable secondary outcomes are seizure types, causes, method of detection, and outcome.

The filters used for subgroup analysis are preterm and term neonates, and a specific geopolitical zone in Nigeria. The effect size for the primary outcome is prevalence. Effect sizes for secondary outcomes are categorical and numerical.

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,PsychInfo, Web of Science, Scopus, and Research Gate.

Search strategy

The search strategy will include MeSH terms, text words, and entry terms and keywords of the PICO components of the research question. An Example of the search strategy to be used in the databases include (infant OR newborn) OR (Neonatal) AND (seizures) OR (Seizure) OR (Convulsion) OR (Jerking) OR (Fits) AND (Nigeria) OR Nigeria*) and this will be modified according to the peculiarities of the database searched. Also, the same search strategy will be applied with every single state and geopolitical zone in Nigeria included in the search terms

Data extraction and Management

The data will be managed using Endnote version 20, Microsoft Excel 365, and Stata 16 IC.

a   Screening: Searched primary studies will be screened in Endnote version 20. They will then be screened by titles and abstracts and duplicates removed.
b   Reviewers: Six reviewers are involved in this study. A pair of reviewers will independently screen studies from each database using Endnote version 20 and Microsoft Excel 365. Conflict will be resolved by a third independent reviewer. All reviewers will be blinded.
c   Selection of studies: This will be done in Microsoft Excel 365 based on the predefined study characteristics, study design, inclusion, and exclusion criteria. Full articles of the included articles will be downloaded and read and their references hand-searched for further references. Authors of eligible studies with missing data will be contacted via email and telephone. The screening and selection workflow will be reported using the PRISMA flow diagram.[32]

Data extraction

The following data will be extracted from each eligible study into a predefined data template in Microsoft Excel

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365 spreadsheet:
i First author's surname
ii Year of publication of the study
iii Year of study
iv State
v Geopolitical zone
vi Sample size
vii Gestational age
viii Seizure prevalence/incidence
ix Gender
x Time of seizure onset
xi Type of seizure
xii Causes of seizure
xiii Method of seizure detection
xiv Outcome of seizure
xv Subgroups: preterm and term neonates, Specific geopolitical zone

Data items (Main measurable outcomes)

The measurable data items in this study will include:
- The overall pooled prevalence of neonatal seizures
- The prevalence of neonatal seizures in term neonates (GA > 37 completed weeks)
- The prevalence of neonatal seizures in preterm neonates (<37 completed weeks)
- The type of seizures (subtle, focal clonic and multifocal clonic, myoclonic and tonic) in preterm and term neonates
- The causes of seizures in preterm and term neonates (hypoxic-ischaemic encephalopathy (HIE), hypoglycaemia, hypocalcaemia, CNS infections, intracranial haemorrhage, congenital malformations).
- The method of seizure detection in preterm and term neonates (clinical alone, EEG alone, clinical and EEG, video-EEG monitoring, and early neuroimaging).
- The reported proportion of preterm and term neonatal deaths from identified seizures.
- The proportion of neonates discharged home without anticonvulsants.
- The proportion of neonates discharged home on anticonvulsants due to persisting seizure.
- The proportion of neonates who developed neurologic deficits from neonatal seizures.

Quality assessment

The Joanna Briggs Institute Critical Appraisal Checklist for Prevalence Studies will be used to critically appraise and assess each of the papers to be included for the quality of the studies concerning their study design, conduct and analysis, and reporting of the studies.[33]

Risk of bias

The Newcastle-Ottawa Scale (NOS) for Assessing Quality of Studies Included into Meta-Analyses if meta-analysis will be carried out.[34]

Studies with extreme bias will be excluded after assessment in the following areas:

1. Method of testing and reporting at the outcome level
2. Reporting primary outcome in the study: prevalence with confidence interval or number of CTs per annum and sample size, as reported at the outcome level
3. Heterogeneity will be assessed at the study level
4. Publication bias will be assessed at the study level
5. Sensitivity testing using include/exclude function at the study level

Data synthesis

- Studies that passed the methodological quality assessment will be included for narrative and data synthesis. The results will be presented in tabular format in addition to a narrative synthesis.
- Data items for both primary and secondary outcomes will be extracted into a predefined template and quantitative analysis done using Stata 16 IC. The pooled prevalence of neonates with seizures will be reported. Reported subgroup analysis of moderating effects of age, gender, gestational age etiology, response to anticonvulsants will be done. Random-weighted meta-analysis shall be carried out. Stata 16 IC will be used to analyze data and inter-study heterogeneity will be explored using Cochran's Q and I-squared statistics. As a rule of thumb, I-squared values of less than 40% will be considered low heterogeneity while values > 40% but < 75% will be considered moderate and values > 75% are high. Also, inverted funnel plots will be used to assess publication bias. Meta-regression will be conducted to assess etiological factors and confounding variables. The pooled effect size and subgroup analysis will be reported in forest plots.

Results

The study selection process will be summarized in a flow diagram according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2015 Statement[32] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA -P) Checklist.[32] A tabular summary of included studies with extracted data items such as the number of neonates with seizures, gestational age, gender, time of seizure, cause of the seizure, and the outcome will be reported. The pooled prevalence of neonatal seizures, 95 % CI, standard error, P values, and 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 done. Forest and regression plots to show sub-group analysis will be included.

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Discussion

The pooled prevalence of neonatal seizures as well as the pooled prevalence in preterm and term neonates will be discussed. The discussion will also examine the type of neonatal seizure, method of its detection, and outcome in neonates. Extensive discussion on the causes of neonatal seizures and ways of prevention will also be done. The final study will be published in a peer-review journal and the findings will be submitted to relevant health authorities to guide policy decision making.

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