Study Protocol

Efficacy of Ayurveda Interventions specifically on weight gain in the Management of Protein Energy Malnutrition in Children: A Systematic Review Protocol

ABSTRACT

Background: In a developing country like India, Protein Energy Malnutrition (PEM)remains a significant and challenging public health issue despite implementing different nutritional policies over the period.It is also accompanying with aggravated risk of all-cause morbidity, as well as fatality due to different diseases in children. The specialized branch of Ayurveda i.e., *Kaumarbhritya* mentions about various nutritional disorders such as *karshya*, *balashosha*, *phakka*, *yakshma*which are having similar symptomatology and treatment approach as that of the PEM.Several clinical studieshave been conducted and are under trial in the field of Ayurveda to explore an effective treatment modality to combat PEMin Children.

Aim: A systematic review to evaluate the efficacy of Ayurveda Interventions specifically on weight gain in the Management of Protein Energy Malnutrition in Children.

Materials and methods: A systematic review which willevaluate published clinical work of Ayurveda treatment modalities specifically for weight gain in the management of PEM in children that will involve "The randomized controlled trials (RCTs), multiple-arms clinical trials, quasi-experimental trials(nonrandomized controlled clinical trials which include before and after studies), observational studies (case series and case reports) through databases like PubMed;COCHRANE;AYUSH ResearchPortal (Govt. of India); DHARA; Google Scholar;CAM databases;HerbMed;Scholarly exchange; Free Medical Journals data base; official publications (journals) found in various Indian societies / associations;NISCAIRproject register, IndMED, for ongoing trials- clinical trial registry of India- ctri.nic.in;Baghels thesis list- researches in Ayurveda;ARD;Conference proceedings/ reports/ compendia and hand searchesto fetch complete available literature." The work of selection of the studies, data extraction, and synthesis will be taken up independently by the

researchers, and two reviewers will try to findout disagreements. Established guidelines for study selection, quality assessment, and narrative synthesis will be followed.Risk of bias assessment will be performed with the help of best online available tools. A protocol will be designed that will ensure transparency for the completed review.Results ofthe study will be elaborately synthesized.The data will be presented in percentage, count and frequency; and if we find the data to be sufficiently homogeneousthen meta-analysis willbe carried out.

Conclusion: The results obtained from this systematic review will be useful in identifying the evidence-based efficacy of Ayurveda interventions on weight gain in the Management of PEM. It will also provide substratum for future research studiesfor generating good-quality evidence that can be helpful to design new health policy to combat PEM effectively.

Keywords: Ayurveda, PEM,children, weight gain,*Karshya,Balashosha, Phakka,Yakshma,*Systematic review protocol.

Introduction: Protein-energy malnutrition (PEM) (International Classification of Diseases 10: E44), remains a significant and challenging public health problem among paediatric age group in developing country like India in spite of implementing different nutritional policies to overcome it. The global scenario estimates that 161 million children under five-year of age are suffering from malnutrition and this condition is worsening in India which is densely populated anda developing country[1]

According to latest National Family Health Survey 4 (NFHS-4), it has revealed that in India 7.5% of the under 5 children are severely wasted, 38.4 % are stunted & 35.7% are underweight, representing 31% and 43% of all the developing world's burden, respectively[2].

Millions of children are affected by malnutrition, some get disabled while for some it turns out to be life threatening. it often causes many diseases and disability in the survivors and restricts millions of children from conquering their growth, development and fullest of intellectual capabilities.

The World Health Organization (WHO) defines PEM as range of pathological conditions arising from coincidental lack in varying proportions of proteins and calories, occurring most frequently in infants and young children, and commonly associated with infection[3].

The Government of India has been putting in incredible efforts under the various nutritional programs like ICDS,(https://icds-wcd.nic.in/guide.aspx)[4] VCDC, etc. for malnourished children. Due to these efforts a decrease in the cases of malnourished children has been seen over the years, but still India has highest burden of PEM as compared to other developing countries.

Emaciated clinical condition of malnutrition closely resembles to *karshya*[5-6],*balashosha*, *kuposhanajanyavyadhi*, *phakkaroga*, *shosha*[7], *yakshma* as mentioned in the classical texts of *Ayurveda* alongwith their management. Hence the same line of treatment[8]. can also be followed for the management PEM. In all the above specified conditions common pathophysiology is mainly vitiation of *vatadosha*[9],*agnimandya*, accumulation of *ama* and *rasavahasrotorodha* resulting in *uttarottara dhatukshaya*. To manage it the drugs which have *vatashamaka, amapachaka, deepana, brimhana, srotoshodhana, dhatu poshaka* and *rasayana* properties should be used, which will provide nourishment to the dhatus, and ultimately will be beneficial in treatment of PEM.

The present best available management followed in nutritional programmes launched by Government of India is standard diet therapy including feeding of energy dense and protein rich food. The recovery with diet is gradual, with minimal significant change in morbidity. Thus, it is the need of hour to standardize and implement an effective management protocol having prompt recovery which can help children suffering from*karshya*, *balashosha*, *kuposhanajanyavyadhi*, *phakkaroga*, *shosha*and PEM without leading to any further complications. In the recent years multiple studies have been conducted in the field of Ayurveda on PEM and significant results have been found in terms of efficacy.

However, till date, no comprehensive systematic review has been undertaken to assess the quality of studies published and clinical efficacy of Ayurvedic treatments. Hence, the present systematic review is undertaken to explore the role of Ayurveda interventions specifically for weight gain in the management of PEM in children.

Review Question: Are Ayurveda interventions effective specifically on weight gain in the Management of Protein Energy Malnutrition in Children?

Objectives:

- To evaluate the efficacy of Ayurveda interventions in the Management of Protein Energy Malnutrition in Children

- To evaluate the effect of Ayurveda Interventions specifically on weight gain in children suffering from PEM.
- If a large number of clinical trialswith homogenous data are available, meta-analysis will be performed

Materials and Methods: This systematicreview protocol has been designed following the PRISMA-P (preferred reporting items for systematic review and meta-analysis protocol) statement guidelines.[10].

This systematic review will be performed using the principles of The Cochrane Handbook for Systematic Reviews of Interventions,[11]. Patients will not be enrolled in any phase of the study.

Inclusion Criteria:

- The review will include "randomized controlled trials (RCTs), controlled clinical trials (CCTs), parallel-group trial, and multiple arms clinical trial, case-series, case reports. Postgraduate and PhD dissertations and other unpublished clinical dataif it contains sufficient data for critical evaluation."
- There will be no restriction with respect to language, if the study is in any other language other than English, then original authors will be contacted,or an attempt will be made to find a translation of the manuscript.Before the final analysis,search will be rerun &further studies will be reanalysed for inclusion.

Exclusion Criteria:

- Non-randomized controlled trials, quasi randomized controlled trials & trials that do not offer detailed results will be excluded from the study.

Type of Participants: Studies with participants of both sex between 6 months to 6 years having classical signs and symptoms of *karshya*, *balashosha*, *phakka*, *yakshma,kuposhanajanyavyadhi*as explained in various classical texts of *Ayurveda*& Protein Energy Malnutrition will be included. Studies including Patients having PEM with Grade I and Grade II as per the WHO standards (MAM and Uncomplicated SAM) will be included.

Type of Interventions: Ayurveda treatment advised for *karshya*, *balashosha*, *phakka*, *yakshma,kuposhanajanyavyadhi* as per the classical text of Ayurveda precisely in the form of *Samshamana* and/or *Shodhanakarma* line of treatment.In this study, Ayurveda treatment which mainly comprises of any internal or external application of herbal, mineral, poly-

herbal, Herbo-mineral drug: single or compound, described in classical Ayurveda literature or a novel drug with ingredients described in Ayurveda texts.

Type of Comparators:

Ayurveda treatment with any form of drug, respective dosage form, dose, schedule, treatment other than Ayurvedic interventions, or combination of both i.e., Ayurvedic and non-Ayurvedic interventions, conservative treatment, placebo/ sham therapy, waitlist controls, no treatment.

Types of Outcomes

Primary Outcomes

- Improvement in cardinal features of *karshya*, *balashosha*, *phakka*, *yakshma*,*kuposhanajanyavyadhi*/PEMspecifically on weight gain.
- Consequent shift/transition of children from SAM to MAM to normal category.

Secondary Outcomes

- Improvement in Laboratory parameter such as Serum protein values.
- Improvement in other anthropometric Parameters
- Improvement in morbidity specifically, time to recovery, hospitalizations during the treatment phase.
- Number of participants withdrawn from the clinicalstudydue toineffectiveness or adverse event of treatment.

Data Sources: List of electronic databases that will be searched: "Medline via PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials), INDMED database, AYUSH Research Portal (Government of India).Manual search in central and departmental libraries of Institute for Post Graduate Teaching & Research in Ayurveda(IPGT&RA)and Ayurveda Research Database by Prof MS Baghel." References gathered from the manuscripts searched through electronic database; and a thorough snowballing of the studies will be carried out to extract all possible data. Author or Authors will re-evaluate the search before the final analyses is made and further studies will be reanalysed for inclusion.

Search Strategy: An Attempt will be made to search all relevant clinical trials available online and off-line published till date. The list of electronic database that will be searched

online through databases like "PubMed, COCHRANE, AYUSH Research Portal (Govt. of India), DHARA, Google Scholar, CAM databases, HerbMed, Scholarly exchange, Free Medical Journals data base, official publications (journals) of various Indian societies / associations, NISCAIR project register,IndMED, for ongoing trials- clinical trial registry of India- ctri.nic.in, Baghels thesis list- researches in *Ayurveda*, ARD, Conference proceedings/ reports/ compendia and hand searches to fetch complete available literature which will include selected journals of Ayurveda including the Journal of Research in Ayurveda and Siddha, Journal of Ayurveda, Ancient Science of Life, Journal of Drug Research in Ayurvedic Sciences, and AYU (an International Quarterly Journal of Research in Ayurveda)" to aid the electronic search.Laterthe bibliographic references of all the trials included will be reviewed to identify other studiesrelevant to weight gain in children suffering from PEM. Authors of the trial studies and experts in the fieldwill be contacted as and when required.

The key terms will be searched relating to or describing the intervention "Ayurved,""Ayurveda" in combination with search term describing condition of the disease "*balashosha*", "*karshya*", "*kuposhanajanyavyadhi*","*phakkaroga*", "*shosha*", "*yakshma*" "PEM." Specific filters will be used to search terms in database search by adaptation. The following search algorithm will be adopted ["AYUSH" OR "Ayurvedic medicine" OR "Medicine, Ayurveda" OR "Ayurved" OR "Ayurveda" OR "Ayurvedic" OR "Ayurvedatherapy" OR "Ayurvedaintervention" OR"Ayurvedic drugs"OR "Ayurveda Herbs" OR "Ayurveda Plants" OR "Ayurvedic Formulation" OR "Ayurveda Panchakarma" OR " Basti" OR "*Santarpana*" OR " *Brimhana*" OR "*Rasayana*" OR "CCRAS" OR "INDIAN TRADITIONAL MEDICINE", OR "*Kaumarbhritya*" OR "*Balaroga*"] AND ["PEM" OR "pem" OR "Protein Energy Malnutrition" OR "CHILDREN" OR "CLINICAL TRIAL" OR "WHO" OR "IMMUNO-MODULATOR" OR "INDIAN ACADEMY OF PAEDITRICS" OR "Weight gain in Children" OR " Anthropometry" OR " Serum Protein" , OR "Z Score" OR "SAM" OR "MAM" OR "ICDS" OR "SUPPLEMENTRY NUTRITION PROGRAMME"] as title/abstract/keyword.

Data Collection and Analysis

Data Management

Once the data is extracted from all the available sources, it will bekept secured.A copy of the data will be stored in an external data storage deviceand to google drive. Only authors of the presentsystematic review will be permitted to access the data.

Selection of Studies: Three of the review authors (SK,RR,BR),will be ear-marked to assess titles and/or abstracts of studies reanalysed using the searchstrategy and those collected fromother additional sources. After excluding duplicates from eligible articles, full-text articles will be screened thoroughly to determine whether they fit into theinclusion and exclusion criteria as stated above. Any contradiction facedto decide the eligibility of particular studies will be resolved throughdiscussion with reviewer (HH). If any of the essential data isfound missing/or incomplete/unclear or to be sought from particular study, trial author will be contacted via e-mail or telephonefor getting exact details. If records are unable to be obtained from theconcerned author,the study will be discarded. Discarded/excluded studies will be documentedwith justified reasons for their omission. Theselection processdetails for the study willbe shown in Preferred Reporting Items for Systematic Reviews andMeta-analyses (PRISMA) flow diagram.

Data Extraction/Collection

Three reviewers (SK, RR, BR) will do screening for the eligibility of the searched studiesindividualisticallybased on inclusion and exclusion criteria. PICO format will be followed to extract data from theincludedstudies. if the available data is incomplete or unclear, thecorresponding author of the clinical trial will be contacted to get the exact information orfor further clarification.

Risk of Bias (Quality) Assessment: The study methodology of included randomized controlledtrials (RCTs) will be assessed by using revised tool availableonline(RoB 2) for the assessment ofthe risk of bias of randomized trials [12]. Apredefined algorithms will be followed to assess five domains of each study, i.e., randomization process,deviations from specified interventions, deleted outcome data,measurement of the primary and secondary outcome, and selection of the enlistedresults. In case of any disagreement,it will be resolved by discussion.

Data Synthesis: meta-analysis will be done if sufficient studies are found homogenous with studies related to weight gain in children suffering from PEM[13]. Fordichotomous data, risk ratio will be used.with 95% confidence interval thetreatment effect will be measured by calculatingthe meandifference for continuous outcomes measure. For trials with Heterogeneity, it will be assessed by statistical chi-square test andusing the I2 statistic.heterogeneity will not be considered if $I2 < 50\%$, whereas significant heterogeneitycan be considered if $I2 \geq 50\%$. Random-effects model will be used if significant

heterogeneity is observedin clinically meaningful studiesfor combination of studies. Fixed-effects model will be used in case of insignificantstatistical heterogeneity. Meta-analysis will be conducted using available software tools to minimize the errors. If meta-analysis is not possible due unavailability of homogenous trial,results will be summarized as systematic qualitative synthesis.

Ethical Clearance: Formal ethical assessment andapproval is not required for this review, as no intervention will be carried out on individual or confidential participant.

Result:(PRISMA)guidelines will be followed for Reporting of the results of systematic reviews and meta-analyses.Further publication will be done in an indexed, open-access peer-reviewed journal.Presentation will be delivered at various national and internationalsymposium to ensure wider propagation of the study.

Discussion: After thorough search it was found that,no systematic review has been carried out to study the effectiveness of Ayurveda intervention in children suffering from PEM specifically on weight gain. This systematic review will draw an inference for evidence-based effectiveness of Ayurveda treatmentand will help to generate database to explore further areas of research.The proposed protocol can be used as a substratum for regenerating same results in a scientific manner for the systematic reviewof PEM in children. We will be strictly adhering to PRISMA-P guidelines while executing the systematic review. The Publication will be a torch bearer to researchers for their further studies. An awareness module can be prepared to prevent *Karshya, balashosha, phakka, yakshma, kuposhanajanyavyadhi*and PEM. The outcome results if promising may be implemented as cost effective, conservative, additive and palliative management to provide references formaking decision from policy makers of Nutritional Health Policy and Programmes at the State and National level.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors

NOTE:

The study highlights the efficacy of " Ayurveda " which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

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