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STUDY PROTOCOL **OPEN ACCESS**

PROTOCOL FOR A MULTICENTER, CONTROLLED, TWO-ARM CLINICAL STUDY EVALUATING THE EFFICACY OF AYURVEDIC THERAPEUTIC INTERVENTIONS AND SWARNAPRASHANA FOR AUTISM SPECTRUM DISORDER IN CHILDREN

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ABSTRACT:

Introduction: ASD is a neurobiological disorder with an early childhood onset characterised by Impairment in social communication and social interaction accompanied by restricted and repetitive behaviours. Surge in prevalence of autism in last two decades gained more attention to look for effective management and very limited research studies are available in the management of autism through *Ayurveda.* There is a need for studying effectiveness of *Ayurveda* therapy in wider population to draw some inferences regarding effectiveness of same. Autism manifestations can be correlate with *doshaja unmade lakshanas* and by considering the *tridosha* with *rajo, tamodushti* and *Agni dushti* in causation of *unmada, Chikitsa* targeting *dosha shamana* and correction of *Agni* was considered for current clinical trial. **Methods:** The current trial comprising of 46 diagnosed children of autism, where trial group will receive selected *Ayurveda* treatment such as *Udgarshana, Sarvanga Parisheka*, *Matra Basti,* and *Narthaki samvahana* with oral administration of *Swarnaprashana* for a period of 90 days. The participants in the control group will receive Occupational Therapy at Academy for severe handicap and autism (ASHA) for a period of 90 days. **Conclusion:** The result could potentially aid in establishing therapy based *Ayurveda* intervention with oral administration of *Swarnaprashana* to be effective as occupation therapy in the management of autism.

Trial registration: Clinical trial registry of India (CTRI – CTRI/2023/06/053937)

Key words: Autism Spectrum Disorder (ASD), Ayurveda, Gut manifestation, ISAA, Sensory abnormalities, Swarnaprashana.

BACKGROUND AND RATIONALE:

Autism spectrum disorder (ASD) is a neurobiological disorder with onset in early childhood, present with impairment in social, communication and social interaction accompanied by restricted and repetitive behavior. [1] Epilepsy, depression, anxiety and attention deficit hyperactivity disorder as well as challenging behaviors commonly co-exist with autism.[2] In India, the estimated ASD prevalence is 0.20%, i.e., 1 in 500 or more than 21, 60,000 people of India. Incidence rate approx.1 in 90666 and total incidence is 11,914 people in India.[3] ASD is more common in males with male female ratio 4:1.4.This social stigma is known to have no satisfactory treatment options till now, applied behavior analysis (ABA), yoga therapy, music therapy, nutritional modifications and certain drugs have shown improvements in some aspects of the disease in various case studies but a significant result has not yet attained.[4] There is no standard treatment modality which addresses all the impairment along with gut issue. Risperidone and Aripiprazole are only FDA approved medications for ASD, and they are approved only for treatment of irritability in 5–16-year-old with ASD, no medications are currently established to treat ASD core symptoms. [4] Very few researches been done in *Ayurveda* and has shown significant improvement inattention and social interaction. Two published case reports have shown improvement in sociability, sensory, behavior and physical conditions. [4] [7] However evidence based studies on Ayurveda therapy in substantial population is not available. New research points to a possible link between autism spectrum disorder (ASD) and the Dysbiosis i.e. altered composition of gut micro biota as many autistic children have co-occurring gastrointestinal problems like constipation, diarrhea.[5] Many studies reports that pro biotics alleviate the progression of autism and reduce cognitive and behavioral deficits that is improved gut health decrease the symptoms in autism.[6] In *Ayurveda* there are hardly any researches done addressing the *Agni* in gut issues in autism and its role with respect to gut brain axis.[4] Thus, there is a need for studying effectiveness of *Ayurveda* therapy in wider population to draw some inferences regarding effectiveness of same. This research aims to treat impairment in social interaction, repetitive behavior, speech, language communication along with consideration to *Agni* with selected *Ayurveda upakrama* such as *Udgarshana*with *siddharthakasnanachurna* [8] *Sarvangaparisheka* with *dashamoolakshaya* [9] Matra basti with *changeryadighrita* [10] *swarnaprashana* [11] and *narthakisamvahana.*[12] This study would be of first of its kind to compare *Ayurveda* therapeutics over Occupational Therapy in children with autism spectrum disorder. If proven useful, this can lead to more effective treatment modality for managing Autism

OBJECTIVES:

1. To evaluate the effect of selected *Ayurveda t*reatment modalities with oral administration ofswarnaprashana on behavior manifestation, social relationship and reciprocity, emotional response, impairment in cognition, speech and communication.

2. To compare the effect of selected *Ayurveda* treatment modalities with oral administration of *swarnaprashana* in study group with occupational therapy in control group based on scales like ISAA, CARS, *Manobhava pareeksha* graded scale.
3. To evaluate the effect of selected *Ayurveda* treatment modalities with oral administration of *swarnaprashana* on gut manifestation based on Subjective symptomatic grading of gut manifestation.

Trial design:

It is an open label, controlled, multicentre clinical trial with two parallel groups of 3 months study.

Study setting:

Both the groups will receive treatment from two different centres. Trial group will receive the treatment consisting of *Ayurveda* procedure based therapies and oral administration of Swarnaprashana from SDM Institute of *Ayurveda* and Hospital, Bangalore. The control group will receive Occupational therapy as practiced at Academy for Autism and severely handicapped (ASHA), Basaveshwarnagara, Bengaluru.

Eligibility criteria:

ICD – 10 – F84.0

Patients must provide written, informed consent before any study procedures occur.

Inclusion criteria:

- Children aged between 3-12 yrs present with manifestation of autism spectrum disorder
- Children of either gender fulfilling the DSM-5 criteria[13] and who pass M-chat.[14]
- Parents who voluntarily agree to participate their child in the study and ensure strict adherence thesame will be included in the study

Exclusion criteria:

- Children with epileptic syndrome and language regression
- Children with ASD along with underlying structural abnormalities (Tuberous sclerosis, primary epileptic abnormality)
- Children with uncontrolled seizures
- Children with whose parents are not willing to participate

Intervention:

Table .No 1. Trial group interventions:

Si.No	Procedure	Drug	Classical reference
1.	*Udgarshana*	*Siddharthaka churna*	*Charaka samhitha ,Kushta Chikitsa[8]*
2.	*Sarvanga parisheka*	*Dashamoolakashaya*	*Suhruthasamhitha, sutrasthana [9]*
3.	*Matra basti*	Changeryadighrita	*Bhaishajyarathnavali, Grahaniroga Chikitsaprakarana.[10]*
4.	Oral administration	*Swarnaprashana*	*Astanga Hridaya, uttara tantra, Balopacharaneeyamadyaya[11]*
5.	*Samvahana*	*Narthaki*(Fingermillet)[12]	

Control group:

Occupational therapy as practiced at Academy for Autism and severely handicapped (ASHA), Basaveshwarnagara, Bengaluru.

Outcomes:

Primary outcome measure: Changes in presentation of autism will be assessed using ISAA and CARS, Manobhava pareeksha symptomatic grading scale.

Secondary outcome measure

Changes in gut manifestation will be assessed based on subjective symptomatic grading.

Sample size:

Sample size: 46, Sample size is derived from formula

n=Zα2XSD2 / precision where n= sample size

Zα=1.96 for 95% confidence level

SD= Assumed Standard deviation (obtained from previous research) as 4.04

Precision e = Zα2X Standard deviation / √n, n= sample size by previous study

n= 19 and SD= 4.04 from previous study, using this precision= 3.38

Sample size for current study will be 21

Considering 20 % dropouts rate N=n/(1-d) i. e. 2

Hence, for the current study, sample size (N) =23 for each group

Recruitment:

For study group - 3to12 years old children with the manifestation of autism spectrum disorder attending Kaumarabhritya outpatient department and in patient department of SDMIAH, Bengaluru.

For control group - 3 to 12 years old children with the manifestation of autism spectrum disorder attending Academy for severe handicaps and Autism (ASHA) for occupational therapy, Basaveshwarnagara, Bengaluru.

METHODS:

Study design – Interventional, Prospective controlled, open label, double arm and black box design.

Data collection methods:

Data will be collected through the specially designed Case Report Form (CRF) and the assessment tools consisting of ISAA (Indian Scale for Assessment of Autism), CARS (Childhood autism rating scale), Subjective symptomatic grading of gut and *Manobhava pareeksha*.

Data management:

Data collected will be entered in the Case record proforma specially designed for the study by the researcher and will be later transferred to MS office excel and SPSS version 20.

Statistical methods:

For statistical analysis, the data will be obtained using Case Report Form (CRF) designed by incorporating all aspects for the study and will be compiled on to a MS Office Excel Sheet. Data will be presented in tabulations and an Analysis will be done using SPSS version 20.

Descriptive Statistics: Frequency, mean, standard deviation and standard error; median and percentile

Inferential Statistics: Inferential statistics will be done by fixing level of significance at $P<0.05$.

Non-parametric test: Wilcoxon-signed rank test- Subjective data will be assessed before and after treatment differences within group.

Mann Whitney U test –will be assessed between the trial and control group.

Freidman test –for multiple comparisons of more than 2 sets within the same group

Parametric test: Unpaired t – test for objective data, assessed between groups Paired t – test will be assessed within group before and after treatment.

Categorical data would be assessed with Chi-square test.

Effect size will be assessed.

Data monitoring:

The researcher and guide will oversee data to ensure adherence to intervention protocols, any adverse effects, and enrolment of the participants. Data will be submitted periodically to the research and data monitoring committee of the department. This committee will review the progress, data integrity, and compliance of this trial at regular meetings. The committee will further have the power to run data audits and interim analysis when appropriate. The Ethical Review Board will be timely informed by the principal investigator any changes regarding study methods or treatment. Ragi stimulation activities conducted at home will be consistently monitored via electronic media.

Safety measures and managing adverse effects:

Although serious side effects are not anticipated from the protocol, any unexpected events that arise during or after the intervention will be recorded and will promptly inform the appropriate specialists. The therapist will document any adverse reactions related to therapy in their records and subsequently report these to the lead investigator. Prior to the intervention, parents will be asked about any known food allergies and briefed on possible side effects from oral medications and therapies so they can inform the principal investigator as soon as possible if any issues occur. Any notable adverse effects will be thoroughly documented and included in the final trial report.

Ethical issues and informed consent:

On 27 October 2022, the Institutional Ethics Committee of Sri Dharmasthala Manjunatheshwara Institute of Ayurveda and Hospital (SDMIAH) granted the trial ethical approval (SDMIAH/IEC/54/2022). The trial has been registered prospectively with the Clinical Trial Registry India (CTRI) (CTRI/2023/06/053937). The researcher will adhere to the Helsinki statement, to maintain ethical principles. The trial participants will sign a written informed consent /assent before enrolment. Participation in the trial will be entirely voluntary, and respondents may withdraw at any time without impacting their treatment. Upon completion, the trial data will be accessible to the primary investigator, data auditors, and authors. Should any adverse effects occur, post-trial care will be provided. Research findings may also be shared via publication in open-access peer-reviewed journals and presented at conferences.

Study status:

Study is ongoing.

Dissemination:

Upon completion of the trial, a research paper detailing the original findings will be submitted to an indexed journal for publication. In addition to this, a seminar will be held to present the results to key stakeholders. If the study demonstrates

effectiveness, a structured awareness program will also be organized. To ensure broad visibility, the trial results will be made available as open-access.

DISCUSSION:

Autism spectrum disorder is a neurobehavioral disorder with onset in early childhood present as impairment in social communication and interaction with restricted and repetitive behaviour. The presentation of ASD varies significantly from one individual to another and over the course of development for a particular child. According to CDC's Developmental disability monitoring network the recent estimated prevalence of autism aged 8 years is 1 in 44. A community based study in India reported a prevalence of 15/10000(0.15%).The global surge in the prevalence of autism in the last two decades could be due to change made in DSM 5 diagnostic criteria, increased awareness among parents and availability of better clinical services. Some of the Autism Children are associated with Gastro intestinal tract (GIT) presentation like chronic constipation, diarrhoea, and abdominal bloating, colicky pain as a co morbidity which significantly worsen their behaviour and quality of life. Autistic child with GI symptoms have more irritability, social withdrawal and hyperactivity compared to those without the GI issues.There are very less clinical studies or effort been made to record the benefit of Ayurveda therapeutic procedures such as *abhyanga, udwartana, sirodhara, basti karma* etc and internal administration of medication. In this study core symptoms of autism, gut manifestation and sensory abnormalities are addressed by administering the procedures like *udgarshana, parisheka, basti and samvahana* with oral administration of Swarnaprashana based on the classical reference.

Supporting information:

Nothing specific

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