Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 1, 2021, Pages. 3320 - 3329

Received 15 December 2020; Accepted 05 January 2021.

Evaluation of Comparative Efficacy of Brahmi and Mandookaparni in Enhancing Memory of Different Prakriti Healthy Male Children- A Double Blind Randomized Clinical Trial-Protocol Article

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Type of Article- Study Protocol
Conflict of Interest: None
Funding: Self
Trial Registration: CTRI
Name of Registry- Registration No.- Applied for CTRI, number yet to come
IEC Ref. No.MGACHRC/IEC/October-2020/141.

Abstract:

Background- Education is the foundation of knowledge in one's life, but the problems of memory and learning may result in poor school performance as well as early dropouts from the schools. Medhya drugs are being frequently used in the various problems related to memory and low IQ in childhood period. Brahmi is most frequently used among them. Mandookaparni is medhya drug described abreast to Brahmi in various classical texts of Ayurveda. However their comparative efficacy has not been studied thoroughly by randomized trial. Another unexplored aspect of use of these medhya drugs is their comparative efficacy on various prakriti type persons. Thus to assess comparative efficacy of Mandookaparni on memory in different prakriti boys, this study is planned. **Objectives-** To evaluate efficacy of Mandookaparni on memory in children with different Prakriti types and compare the efficacy with that of Brahmi.**Methodology-** The study will be conducted on healthy volunteer boys aged 8-10years of age, recruited through school surveys in nearby

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schools of Mahatma Gandhi Ayurved College, Hospital and Research Centre, Salod, Wardha. The study will be double blind, randomized, standard concurrent control, and parallel group design. The participants will be randomly grouped into two groups of 85 individuals in each group. One group will be given Mandookaparni while other will be given Brahmi, both in Avleha form. The assessment will be made for total memory scale by using PGI memory scale for children.**Expected Results**- The study will validate the efficacy of Brahmi and Mandookaparni in enhancing memory and will give detailed account of their efficacy in different dominant prakriti boys. **Conclusion-** The study will provide initiative toenhance awareness of Prakriti based administration of drugs including Medhya drug. By using inferences from the study, we will be able to ensure utilization of optimum effect of both these medhya drugs.

Keywords-Medhya drugs, Memory, Prakriti, Mandookaparni, Brahmi, Nootropic herbs

INTRODUCTION:

Traditional education is one of the most important building blocks of one's knowledge, career, employment, earnings and life in whole. But problems of learning & memory may results in school absenteeism, poor school performance, early school dropouts and ultimately poor socio-economic condition.[1] Our knowledge and awareness for these problems have considerably improved in last few decades. As of now we have various methods and interventions to make early diagnosis and provide adequate treatment modality to improve school performance of such children. One of recent advancement in this field is use of various herbal nootropic agents. These nootropic drugs had been proven to be effective in improving cognitive capabilities[2] and thus are being employed in problems of low IQ, poor learning and problems related to memory. The most frequently used nootropic drug is Brahmi (*Bacopamonnieri*). It is widely researched for its use as cognition enhancer and is found useful to enhance memory. Another drug namely Mandookaparni (*Centellaasiatica*) is described abreast to Brahmi in classical texts like Samhita,[3,4]Niganthu[5,6] (AyurvedicPharmacopeia's). The side by side description of both these drugs is essentially to emphasize their similar properties as well as therapeutic uses. Recent in vitro studies and animal studies also proves utility of Mandookaparni in enhancing cognition as well as memory functions.[7] However, there are not much conclusive randomized trials to validate its clinical efficacy. In addition, wide utilization of these herbal nootropics (Medhya drugs) without appropriate consideration of Ayurvedic principles of their use may not exploit their potential optimally and may also results in doubts about their efficacy. One of such Ayurvedic principle of use of any drug is assessment of Prakriti and using drugs appropriate for prakriti type. Various drugs are being used for their nootropic effect randomly without analyzing suitability for particular prakriti. On probing for researches on nootropic drugs; addressing their prakriti based use, we do not found any research work done. Thus, the objective of this study is to determine comparative efficacy of Mandookaparni in enhancing memory in relation to Brahmi in different prakriti persons and fill this research gap we have planned this research.

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RESEARCH GAP ANALYSIS

- Brahmi & Mandookaparni are described to have similar properties in various Nighantu namely BhavprakashNighantu[8] and MadanpalNighantu.[9] These both are described to have *Medhya* and *Smritiprada* properties in these above mentioned texts. Thus, they are being increasingly employed in problems of low IQ, poor learning and problems related to memory

- Both Brahmi & Mandookaparni are being frequently used interchangeably. However, more clinical studies have been conducted on Brahmi (*Bacopamonneiri*) and had validated its nootropic properties, but Mandookaparni (*Centellaasiatica)* remains less researched clinically and thus, not proven to have similar properties (nootropic) to Brahmi (*Bacopamonneiri*). Puttarak et al in their review have analyzed few clinical studies on *Centellaasiatica* and report insignificant cognitive effect.[10] However, the clinical studies they had reviewed are not only on *Centellaasiatica* as single drug, but they also include studies of compound herbal preparation containing *Centella*. Moreover, various studies included were conducted with large variation of dosage which may have resulted in insignificant results in meta-analysis.

- Further, different studies showed different level of effectiveness in particular cognitive domain or facet of memory on similar assessment tools e.g. Brahmi is shown to be highly significant to improve digit span (backward) in one study (Barbhaiya, 2008)[11] while ineffective in another study (Roodenrys, 2002).[12] Similarly Brahmi is shown to have highly significant results in Auditory verbal learning test delayed recall (AVLT DR) in one study (Morgan, 2010);[13] significant in another two studies (Barbhaiya, 2008 & Calabrese, 2008)[3,14] and insignificant in another (Stough, 2008)[15]

- These differences in results of medhya drugs could be explained by various Ayurvedic parameters e.g. different prakriti types of the study population, Desha (Place of study), Kala (time of study) etc.However, no studies have been undertaken to assess effect of these medhya drugs in different prakriti persons (mainly in children)

- Thus, to assess comparative effect of both these Medhya drugs on memory of different DehaPrakriti persons, this study is planned

Trial design- This is planned to be an equivalence, Randomized, reference standard controlled, double blind parallel group trial with 1:1 allocation ratio.

METHODOLOGY-

Study Setting- The study will be conducted on healthy volunteer male children recruited through school surveys in nearby schools of Mahatma Gandhi Ayurved College, Hospital and Research Centre, Salod, Wardha. The participants will be randomly assigned into two groups with keeping equal number of dominant dehaprakriti boys in each group.

Participants

Healthy volunteer male children between 8-10 years

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Inclusion Criteria

- Boys between 8-10 years of age
- Children whose parents are willing to participate and sign the informed consent
- Children of dominant Vataj, Pittaj and Kaphaj Prakriti

Exclusion criteria

- Children with subnormal intelligence or having diagnosed mental illness
- Children suffering any acute or chronic illness and/ or taking medication

Intervention

The trial group will be given MandookaparniAvleha in dose of 20g per day in two divided doses with luke warm water while the control group will be given BrahmiAvleha in dose of 20g per day in two divided. The drugs will be administered in the form of Avleha (linctus) for better palatability. Avleha will be made of crude study drug i.e. Powder of Brahmi or Mandookaparni with use of sugar, ghee & honey in ratio of 1:4:0.15:0.15 respectively. The drug will be given continuously for 90 days. The complete schedule of interventions is detailed in table no.1

Table no 1, showing interventions administration with dose details

	BrahmiAvleha (Group A)	**MandookaparniAvleha (Group B)**
Type of formulation	Avleha	Avleha
Dose	20g/day in two divided doses	20g/day in two divided doses
Route of administration	Oral	Oral
Time of administration	Twice daily 1 hr before meal	Twice daily 1 hr before meal
Anupana	Luke warm water	Luke warm water
Duration	90 days	90 days

Discontinuation criteria

- Child or parents not willing to continue or complete study
- Development of any acute illness requiring hospitalization
- Development of severe adverse drug event

Adherence monitoring- The participant will be encouraged to adhere to the study drug and the same will be assessed by telephonic communications as well as assessment of total used drugs at each monthly follow-ups through return of empty containers.

Outcome-The primary outcome measure will be change in total memory score as well as change in score of individual memory tests and domains (working, short term & long term

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memory). The secondary outcome will be varied memory characteristics in various dominant prakriti types and efficacy of both medhya drugs on them.

Study schedule/timeline

The study timelines are explained in table 2 and figure 1

Table no 2 showing study schedule

	Baseline (0 day)	**31st Day**	**61st Day**	**91st day**
Informed Consent & PIS	**YES**			
Medical History	**YES**			
Prakriti Assessment	**YES**			
Memory Assessment	**YES**			**YES**
Assessment of Drug compliance		**YES**	**YES**	**YES**
Assessment of ADEs		**As per standard guidelines**		

Sample Size

There are several methods used to calculate the sample size depending on the type of data or study design**.** As our study is equivalence trial to prove efficacy of Mandookaparni in enhancing memory in comparison to control i.e. Brahmi. We used the following formula (Baoliang Zhong,2009)[16]

$$N = 2\left\{\frac{Z_{1-\alpha/2} + Z_{1-\beta}}{\delta_0}\right\}^2 \times p\,(1-p)$$

Here δ_0 is clinically admissible margin of equivalence and taken as 10%, p is average percentage improvement of control and experimental drug. Percentage improvement in memory score as reported by Stough et al (2008)[2] in their study on *Bacopa*is 6%. Assuming a 5% improvement from *Centella*, p comes out to be 0.055. Thus, putting all these values in the above formula sample size comes out to be 82 with 95% confidence level (α=0.05) and 80% power. Therefore, present study is proposed with sample size of 85 in each group i.e. minimum 170 participants in all. We will enrol 10% extra participants i.e. 9in each group as a cover for any dropouts.

Allocation & Blinding- The participants will be allocated into either group randomly through computer generated random allocation software. The allocation sequences will be generated in advance, which are then sealed in consecutively numbered opaque envelopes.The packing of both the interventions will be kept very identical thereby both investigator and supervisor could not know about intervention. The allocation sequence will be generated by the supervisor and investigator (PhD scholar) will enrol participants as well

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as will assign interventions to them. As it is a double blind study, both participant and investigator will be blinded after assignment to intervention.

DATA COLLECTION, MANAGEMENT, AND ANALYSIS METHODS:

Pre & Post treatment assessment of memory will be done through "PGI MEMORY SCALE FOR CHILDREN".[17] The scale consists of ten subtests, viz. remote memory, recent memory, mental balance, attention and concentration, delayed recall, immediate recall, verbal retention for similar pairs, verbal retention for dissimilar pairs, visual retention and recognition of common objects. It is made in simple Hindi and items are child friendly pertaining to everyday life of children. The test-retest reliability of the scale is 0.82.Data will consequently be transcribed onto a computer database from the score sheets of scale. The database will be prepared in advance in a manner so that it is similar in format to CIF and memory scale, allowing for easy transcription of information.

Statistical methods**:** Assessment parameters will be subjected to Univariate and multivariate analysis using Statistical Package for Social Sciences (SPSS) with appropriate statistical methods.

Adverse Drug Events reporting- All adverse events observed or reported by patients will be appropriately recorded with information about severity and possible relation to the study medication. Any serious adverse effects will be notified immediately to the study monitor.

ETHICS AND DISSEMINATION:

Ethical approval for the proposed study has been taken from institutional ethics committee and its reference number is- Ref. No. MGACHRC/IEC/October-2020/141.

The proposed trial is being registered in clinical trial registry of India.

A written informed consent will be taken from the parents of the participants after giving detailed account of the study objectives and plan of the study. The study findings will be published in relevant journals to disseminate the results for the use of other medical fraternity.

EXPECTED OUTCOMES/RESULTS:

The study will give a detailed account of efficacy of Brahmi and Mandookaparni in different dominant prakriti boys. It will also validate Ayurvedic concepts of varied memory characteristics of various dominant prakriti types.

DISCUSSION

Medhya drugs are frequently used drugs by paediatric practitioners of Ayurveda. Brahmi and Mandookaparni are the most frequently used among all the medhya drugs. These both drugs are described in same context in Ayurvedic classics.[3,4,5,6] This parallel description of these both drugs have resulted in some confusion among various end users. Most of the time they are being used interchangeably by practitioner without knowing exact indication in particular prakriti as well as in disease condition like in the problems of memory, learning, behaviour

etc. Presently Brahmi (*Bacopamonnieri*) has been extensively researched clinically for its nootropic effect and is proven to have good effect on learning as well as memory.[2]While Mandookaparni (*Centellaasiatica*) is less researched clinically and its equivalence to Brahmi for nootropic effect has not been proven yet.However, recent in vitro studies and animal studies have proven utility of Mandookaparni in enhancing cognition as well as memory functions.[18]Further, there is need of evaluation of optimum effect of various Ayurvedic drugs in different persons based on their prakriti types to best employ the principle of individualized medicine. The principle of Ayurveda clearly mentionsthe personalized use of various medicines.[19]

Simultaneously, various RCTs which have shown positive effect of Brahmi on memory are not having similar effect on various tests of memory throughout different studies. Brahmi is shown to be highly significant to improve digit span (backward) in one study (Barbhaiya, 2008)[20] while ineffective in another study (Roodenrys, 2002).[21] Similarly Brahmi is shown to have highly significant results in Auditory verbal learning test delayed recall (AVLT DR) in one study (Morgan, 2010);[22] significant in another two studies (Barbhaiya, 2008 & Calabrese, 2008)[3,23] and insignificant in another (Stough, 2008).[24] These differences can only be explained on the basis of individual response to the drugs administered and are well elaborated in Ayurveda. Ayurveda explains that effect of *Bhaisaja* (drug) is depended on Prakriti, Deshakala etc.[19] Thus, this study is one step to establish differential effect of medhya drug (Brahmi & Mandookaparni) at one end while estimation of effect equivalence of these two drugs on the other.

CONCLUSION:

There is need to enhance awareness of Prakriti based administration of drugs including Medhya drugs. The study may provide initiative in this particular area. By using inferences from the study, we will be able to ensure utilization of optimum effect of both these medhya drugs.

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Table No. 1- Complete dosage schedule of interventions

	Brahmi Avleha (Group A)	**Mandookaparni Avleha (Group B)**
Type of formulation	Avleha	Avleha
Dose	20g/day in two divided doses	20g/day in two divided doses
Route of administration	Oral	Oral
Time of administration	Twice daily 1 hr before meal	Twice daily 1 hr before meal
Anupana	Luke warm water	Luke warm water
Duration	90 days	90 days

Table No. 2-Study schedule/timeline

	Baseline (0 day)	**31st Day**	**61st Day**	**91st day**
Informed Consent & PIS	**YES**			
Medical History	**YES**			
Prakriti Assessment	**YES**			
Memory Assessment	**YES**			**YES**
Assessment of Drug compliance		**YES**	**YES**	**YES**
Assessment of ADEs		**As per standard guidelines**		

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Figure No. 1 Study timelines