Research Article

EFFECT OF *GANDHAKA KALPA* INTERNALLY AND *KSHEERABALA* 101 *AVARTI TAILA NASYA* IN DRY AGE RELATED MACULAR DEGENERATION- A CLINICAL STUDY

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ABSTRACT

Introduction: Age-related macular degeneration (AMD) is a neurodegenerative disease which is one of the leading causes of vision loss affecting population above the age of 50 years. Of the two types wet and dry AMD, dry AMD constitute 90% of cases. Currently there is no effective treatment for AMD except for antioxidant supplementation which can delay the progression of AMD and its associated vision loss. In Ayurveda, it is a *Vata Pitthadhika Drishtigata Roga* compounded by *Dhatukshaya* in *Vardhakya.* The treatment should be *Brimhana, Chakshushya and Rasayana* to tackle the degenerative changes. *Gandhaka Kalpa* from *Rasaratnasamucchaya* and *Ksheerabala* 101 *Avarti Taila* has these properties to ameliorate the disease pathology. Hence a clinical study was planned with the objective to assess the effect of *Gandhakakalpa* internally and *Ksheerabala* 101 *Avarti Taila Nasya* in dry AMD.

Methods: The study design was interventional, pre and post evaluation without control. After preparatory phase*,* patients were given *Nasya* with *Ksheerabala* 101 *Avarti Taila* followed by administration of *Gandhaka Kalpa* with concurrent administration of *Ksheerabala* 101 *Avarti Taila* as *Pratimarsa Nasya*. Study and follow up were done in 30 eyes. Results were documented and statistically analysed using Friedmains's test, paired t test, Wilcoxon's signed rank test and McNemar test according to type of variable.

Result: The intervention is statistically significant while considering visual acuity (p < 0.001) and Daily Living Tasks Dependent on Vision questionnaire scores (p< 0.0001) and not significant for optical coherence tomography and Amsler grid findings.

Conclusion: The intervention is an effective protocol to be followed in Ayurveda for dry AMD.

KEYWORDS: Dry AMD, *Gandhaka Kalpa*, *Ksheerabala* 101 *Avarti Taila*, *Nasya.*

INTRODUCTION

The elderly population, which forms a significant part of the demography, is unique in the sense that they have a set of health problems that are found exclusively in that population. As the age progresses, the sense organs start to deteriorate, thus affecting the quality of life and daily routine of already struggling individuals. Age related macular degeneration (AMD) is such a disease affecting individuals above the age of 50 years. Its prevalence increases with age and is one of the leading causes of blindness in elderly population globally. Dry form of AMD forms 90% of affected cases. Kulkarni *et. al* reported the overall proportion of AMD in Maharashtra was 1.38%.[1] The estimated statistics of people with age-related macular degeneration in 2020 is 196 million, increasing to 288 million in 2040.[2] Hence it is an important public health issue. For such a disease burden, currently there is no

effective treatment except for antioxidant supplementation to reduce the risk of advanced AMD and its associated vision loss. In Ayurveda, it is considered a *Drishtigataroga. Vardhakyaavastha* of age produces *indriya* and *Dhatudourbalyata*. The symptoms of AMD are found in various *Drishtigata rogas.* But it is not possible to limit its clinical presentation to any one of the classically described *Drishtirogas.* It appears to have a *Vata -pitta dosha* predominance with associated *Raktavahasrotodushti.* Here the treatment should be *Chakshushya, rasayana* and *Brimhana* to tackle the degenerative changes. *Gandhakakalpa,* the reference of which is found in *Rasasatnasamuchaya Uparasa niroopanaadhyaya*, is said to bring eye sight as sharp as that of a hawk on internal administration.[3] The *Kalpa* selected here has *Gandhaka, Bhringaraja Swarasa, Triphala choorna* as ingredients. *Nasya* is a *Panchakarma*

procedure indicated especially in diseases affecting head*. Ksheerabala Taila* which is *Rasayana, Jeeevaneeya, Brimhaneeya* and *Indriyaprasadana*[4] is taken for *Nasya* as this is a degenerative disease due to *Dhatukshaya* in body as a result of *Vardhakya* affecting *Darsanendriya.* In Ayurveda, dry AMD is a relatively unexplored avenue for research. Given the neurodegenerative nature of AMD and the lack of a standard effective management in other systems of health care, this area warrants active research. The drugs chosen for the study are safe, inexpensive and have potent antioxidant properties. Hence this study was undertaken as a lacuna was felt in the research related to this disease.

Aim

To study the effect of *Gandhaka Kalpa* internally and *Ksheerabala* 101 *Avarti Taila Nasya* in Dry Age -related Macular Degeneration.

MATERIALS AND METHODS

Study design

Pre and post Interventional trial without control.

Study setting

Department of Shalakyathantra, Govt: Ayurveda College, Trivandrum.

Selection of patients

Patients diagnosed as dry age related macular degeneration (dry AMD) from OPD and IPD of Shalakyathantra, Government Ayurveda College, Trivandrum, fulfilling exclusion and inclusion criteria, 30 eyes in total were selected by consecutive sampling. Study was completed in 24 eyes.

Exclusion criteria

1. Uncontrolled hypertension or diabetes

2. Patients with mature cataract, high myopia, glaucoma, other retinal degenerations

3. Patients with systemic illness like uncontrolled hypercholestremia, liver disease, renal disease

4. Pigment epithelium detachment

5. *Nasya Anarha*

Study tool:

a. Case proforma

b. Modified Daily Living Tasks Dependent on Vision questionnaire (DLTV) questionnaire specific to Macular degeneration

c. Investigations

- LogMar Chart
- Amsler grid
- Ophthalmoscopy
- OCT

Clinical evaluation and investigations was done prior to the commencement of interventions, after treatment and 2 months after treatment.

Study drugs

Gandhakakalpa and *Ksheerabala* 101 *Avarti Taila.*

Ksheerabala Taila was prepared according to standard procedure mentioned in AFI.[5] For preparing *Gandhaka Kalpa, Gandhaka* was first purified by *Kurmaputa* method and later triturated with *Bhringarajaswarasa. Gandhaka Kalpa* was then dispensed in 3g packages by mixing 750mg of purified *Gandhaka* with 2.25gm of *Triphalachoorna.*

Procedure

After obtaining informed consent, all the clinical examination and investigations were done and patients were subjected to intervention after *Poorvakarma* as follows:

Table 1: *Poorva karma*

Treatment	Medicine	Dose	Time	Duration
Sadyasneha	*Plain ghritha*	10gm	8 pm, given with hot gruel	1st day
Virechana	*Avipathychoornam*	20g with honey	6 am in empty stomach	2nd day

Table 2: Schedule of interventions:

Treatment	Medicine	Dose	Time	Duration
Nasya	*Ksheerabala* 101 *Avarti taila Thalam* with *Rasna jambeeram Mukhabhyanga* with *Balathailam*	5ml in each Nostril	8 am in morning Empty stomach	7 days
Internal medicines	*Gandhakakalpa*	3g *Anupana*-8 drops of honey, 13 drops of ghee, 20 ml milk	one and half hours after taking food at night	After *Nasya*, for 2 months.
Pratimarsa nasya	*Ksheerabala* 101 *AvartiTaila*	1ml in each nostril	4 pm	2 months (concurrent with *Gandhakakalpa*)

Outcome variable

1. Change in The Daily Living Tasks Dependent on Vision questionnaire (DLTV) score.
    The DLTV consists of a core of 22 individual items each with a four point ordinal response scale.[6]
2. Change in visual acuity assessed by LogMar Visual acuity chart by noting the change in visual acuity
3. Change in Amsler grid findings:

Assessed using a grading scale.[7]

Grade 0: No distorted vision

Grade 1: Lines are crooked or bent

Grade 2: Boxes appeared different in size and shape from each other

Grade 3: Boxes and lines are wavy, missing.

Changes in OCT in the selected subset:

OCT was taken on Zeiss Cirrhus HD OCT in a subset of 17 eyes.

Retinal thickness in μm above an area with significant drusen was measured.[8-9]

Statistical analysis

Paired T test, Wilcoxon signed Rank test, Freidman's test and McNemar test according to the type of distribution of the variable.

RESULTS

Majority of the patients had *Vata- Pitta Prakruti*, disturbed sleep, *Avara Vyayamasakti*, *Avara Satva* and *Krurakoshta.* Also *Katu Amla Lavana Ahara*, irregular food habits, *Mandagni* and *Heena Abhyavaharana Sakti* was found in a large proportion of patients.

Because there were four outcome variables, the p value was adjusted by using Bonferroni's correction method and therefore significance will be on the basis of p value less than 0.0125.

Analysis of DLTV scores

Table 3: Change in visual acuity according to no. of letters read in Log Mar Chart

| Change in visual acuity	Frequency			Percentage		
	BT-AT	AT to AF	BT-AF	BT-AT	AT-AF	BT-AF
Decreased	0	5	0	0	20.8	0
Unchanged	10	16	11	41.6	66.6	45.8
Improved by 1 letter	0	0	0	0	0	0
Improved by 2 letter	3	0	2	12.5	0	8.3
Improved by 3 letter	2	2	2	8.3	8.3	8.3
Improved by 4 letter	0	0	1	0	0	4.2
Improved by 5 letter	4	1	4	16.6	4.2	16.6
Improved by 6 letter	0	0	1	0	0	4.2
Improved by 7 letter	1	0	0	4.2	0	0
Improved by 8 letter	2	0	2	8.3	0	8.3
Improved by 9 letter	1	0	0	4.2	0	0
Improved by 10 letter	1	0	1	4.2	0	4.2

58.4% patients showed improvement in their visual acuity in the period between before treatment and after treatment. Visual acuity of 42% patients remained unchanged.

Table 4: Log MAR visual acuity analysis

Parameter	N	visual acuity in Log MAR		Paired comparison	Paired difference		Paired t test	
		Mean	SD		Mean	SD	t	p
BT	24	0.470	0.174	BT *vs* AT	0.062	0.067	4.494	<0.001
AT	24	0.532	0.182	BT *vs* AF	0.056	0.062	4.422	<0.001
AF	24	0.526	0.179	AT *vs* AF	0.006	0.047	0.613	0.546

(BT- before commencement of treatment, AT- after treatment, AF- At followup)

Graph No: 1 -Analysis of Log MAR visual acuity
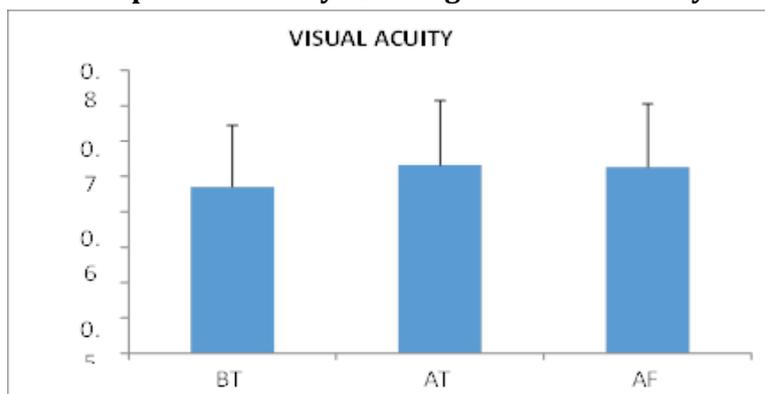
As the p values are less than 0.001, change in visual acuity scores of patients in the period before treatment and at follow up are very significant.
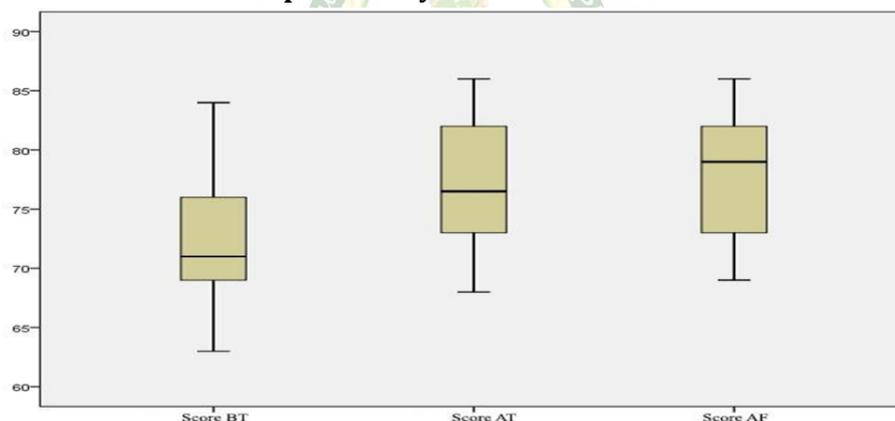
Analysis of DLTV score

Table 5: Analysis of DLTV scores in different points of time

DLTV	BT	AT	AF	Test applied- Friedman's test	P value
Mean	72.286	77.071	78.071		
Median	71.000	76.500	79.000		
SD	6.2071	6.2322	5.6496		
IQR	8	9.75	9.75	$\chi^2 = 23.680$	0.0001

(BT- before commencement of treatment, AT- after treatment, AF- At follow up)

Graph 2: Analysis of DLTV scores

As p value obtained is 0.0001, there are highly significant differences in the DLTV scores measured at the three time points, BT, AT and AF. The change in DLTV scores of patients in the period before treatment and at follow up is very significant.
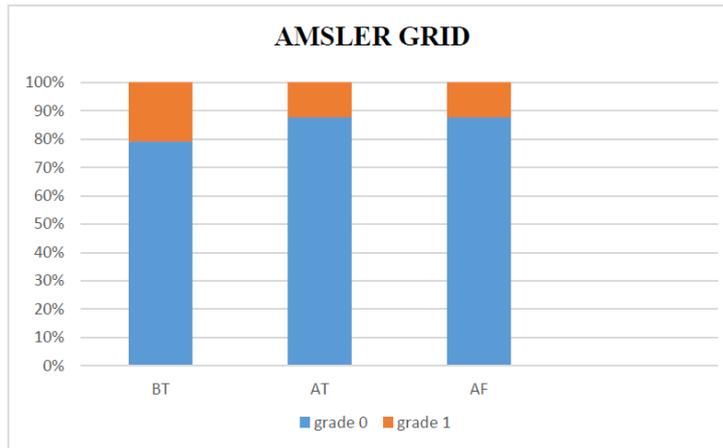
Analysis of Amsler grid findings

Table 6: Analysis of Amsler grid finding

Amsler grid	BT		AT		AF	
	N	%	N	%	N	%
Grade 0	19	79.2	21	87.5	21	87.5
Grade 1	5	20.8	3	12.5	3	12.5
Total	24	100.0	24	100.0	24	100.0
Comparison with BT p			0.500		0.500	

(BT-before commencement of treatment, AT-after treatment, AF-at follow up)

0: No distorted vision, Grade 1: Lines are crooked or bent) McNemar test p= 0.500

Graph no: 3- Analysis of Amsler grid findings

Before treatment 79.2% patients had grade 0 findings in Amsler grid while 20.8% patients had grade 1 findings. After treatment and at follow up only 12.5% patients had grade 1 findings. As p value is 0.500, the change in Amsler grid findings of patients before treatment and at follow up is not significant.
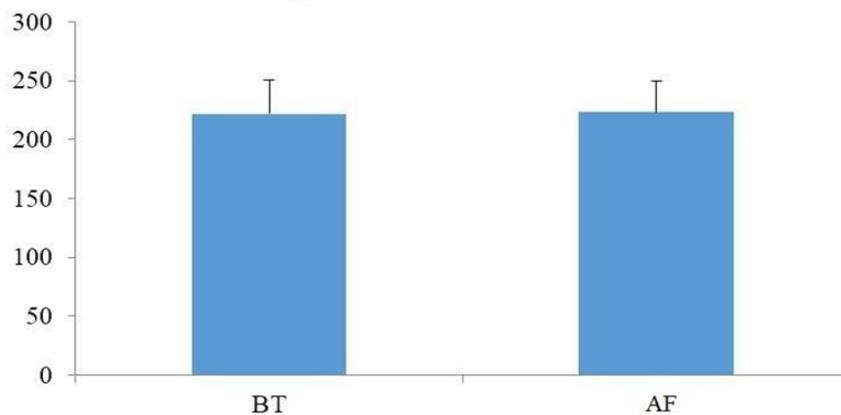
Analysis of OCT findings

Table 7: Analysis of OCT findings

	N	OCT		Paired comparison	Paired difference		Paired t test	
		Mean	SD		Mean	SD	t	P
BT	9	222.0	29.0	BT *vs*AF	1.222	9.909	0.370	0.721
AF	9	223.2	26.1					

Out of 17 eyes, 12 eyes had significant OCT findings of dry AMD. As 3 eyes dropped out, for statistical analysis only 9 eyes were considered.

Graph no: 4- Analysis OCT findings

The mean retinal thickness measured above drusen before treatment was 222±29 μm and that measured at follow up was 223±26μm. The p value obtained in paired T test was 0.721. So this is not statistically significant.

DISCUSSION

Dry age-related macular degeneration is a chronic progressive neurodegenerative disorder. The main mechanisms of its pathogenesis include genetic background, oxidative stress, chronic inflammation, lifestyle and diet. By analyzing *Samprapti* of the disease, dry AMD has a *Vata- pitta* predominance with associated *Raktavahasrotodushti*, and affects individuals in old age. Amongst the study patients, most had *Vata-Pitta Prakruti*. Here the *Prakruti* and disease are both *Vata-pittadhika*. It is possible that *Vata-pittaprakruti* individual may have a predisposition to develop dry AMD. Other patient related data like *Katu, Amlalavana* predominant diet, *Heena Abhyavaharanasakti*, *Mandagni* and irregular food habits seems to be dietary implications causing aggravation of *Vata*. Disturbed sleep, *Avara Vyayamasakti*, *Avarasatva* and *Krurakoshta* points to a predominant *Vatakopa* in the body. The effect of intervention on visual acuity and DLTV score of

patients was linear into the follow up period while it was negligible for OCT findings and Amsler grid.

Probable mode of action of intervention

It can be inferred that the mode of drug action is a conglomerate effort of *Dosha* and *Vyadhiharakarmas* of chosen formulations and their individual components, action of *Nasya karma* and the order of application of interventions.

A comprehensive review of individual drugs of *Gandhakakalpa,* reference of which is found in RRS *Uparasadhaya*, reveals that all the drugs have *Rasayana* and *Chakshushya* properties.[10-13] The *Prabhava* of the *Yoga* is imparting sharp vision equal to that of a vulture. In addition, *Gandhaka* is *Deepana, Madhura* and *Atirasayana. Bhringaraja* has *Amahara* karma.[14] Studies show that *Triphala* could be a potential source of natural antioxidants in preventing or slowing the progression of age-associated oxidative stress-related degenerative diseases.[15] *Eclipta alba* extract also has potent antioxidant properties and protect against neuronal damage induced by oxidative stress.[16] All these properties show that the drugs are *Dosha* and *Vyadhipratyaneeka,* and able to arrest the etiopathological factors. The *Bhavana* of *Gandhaka* in *Bhirngaraja* may also reduce the particle size of the compound thus enabling faster absorption of the drug with greater bioavailability*. Madhu, Ghritha* and milk as *Anupana* helps to assimilate the combination and provide a suitable vehicle for its drug action. Also having *Ghritha* as *Anupana* may make the lipid soluble components of the drug be able to cross the blood brain barrier. Drug absorption by transmembrane fusion across BBB is favoured by low molecular weight and lipid solubility.[17]

Ksheerabala 101 *Avarti Taila*, mentioned in *Vatasonitha chikitsa,* Ashtangahridaya is apt for *Vata-Pittanubandha Raktadushti* as it is *Vata-Pitta Samana.* It is *Rasayana, Brimhana, Jeevaneeya* and *Indriyaprasadana*. All these qualities are *Vyadhi* and *Doshapratyaneeka* and highly relevant to the treatment principles of dry AMD*.* Its individual components, *Sida rhombifolia* and sesame oil have high potential of antioxidant activity and free radical scavenging properties.[18-19] Milk is a rich source of various nutrients. *Goksheera* is *Jeevaneeya, Brimhaneeya, Chakshushya* and *Vata-pitta hara*.[20] Additionally, previous studies have shown *Ksheerabala* to be a neuroprotective agent in diseases induced by oxidative stress.[21]

The drug instilled in the nose is said to act by reaching *Sringataka* and then pervading to eye and nourishing the tissues. Nasal route drug delivery is an attractive strategy for brain targeted drug delivery as it allows therapeutic agents to be delivered to the brain via neural pathways such as the olfactory and trigeminal nerves, thereby bypassing the blood-brain barrier.[22] As the drug used for *Nasya* here is lipid based, absorption can occur through transcellular route as well.[23] Anatomically retina is an extension of CNS. Hence *Nasya* helps to deliver the *Brimhana, Rasayana, Jeevaneeya* and *Indriyaprasadana* properties of *Ksheerabala* 101 *Avarti Taila* to the targeted retina. The patients underwent *Nasya* after *Virechana* and *Gandhaka Kalpa* was administered after both *Kayashudhi* and *Urdhwanga Shudhi.* This makes the target tissues to be receptive to the *Rasayana Gunas* of the drug.

CONCLUSION

Nasya with *Ksheerabala* 101 *Avarti Taila* and internal administration of *Gandhaka Kalpa* is an effective intervention in the management of dry AMD along the lines of Ayurveda. The intervention was safe to use, and economical. A larger sample size would improve the accuracy. Since dry AMD has slow progression, yearly follow up and monitoring with regular measurement of the outcome variables will provide details on the nature of progression of disease in patients who received the intervention.

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