Original Article

Add-on effect of Ayurvedic treatment protocol for diabetic retinopathy: A randomized controlled clinical study

V. Krishna Kumar[1,2], B. Vaghela Dharmendra Singh[2], Rajagopala Manjusha[2,3]

[1]Department of Ayurveda, Regional Ayurveda Research Institute for Eye Diseases, Lucknow, Uttar Pradesh, [2]Department of Shalakya Tantra, Institute for Post Graduate Teaching and Research in Ayurveda, Jamnagar, Gujarat, [3]Department of Shalakya Tantra, All India Institute of Ayurveda, New Delhi, India

Abstract

Background: Diabetic retinopathy (DR), the leading cause of visual disability in diabetics, is a significant complication of diabetes mellitus. Currently available conventional treatments for DR have certain limitations, considering which Ayurvedic treatment protocol was designed. **Aim:** The aim of this study was to evaluate the clinical efficacy of the Ayurvedic treatment protocol for DR. **Materials and methods:** This was a randomized, controlled, black box design clinical study conducted from April 2016 to September 2017 by the department of Shalakya Tantra of a tertiary academic hospital in Western India. A hundred patients of DR in the age group 30–70 years were randomly divided into two groups by simple random sampling using computer-generated random number tables. In the trial group (n = 70), the preparatory phase included *Dipana-Pachana* (stomachic and digestant), *Koshtha Shodhana* (mild therapeutic purgation), and *Shiro Virechana* (eliminative nasal medication). The treatment phase included *Marsha Nasya* (nasal medication) and *Pratimarsha Nasya* (nasal medication of mild dose) with *Durvadi Ghrita*, *Takra Dhara* (pouring medicated buttermilk over the scalp) with *Siddha Takra*, and intake of *Rasayana Yoga* (treatment duration – 3 months). In the control group (n = 30), patients were kept under conservative treatment and observed during the trial period of 3 months. Patients of both groups continued with their treatment for diabetes and DR if any. Two follow-ups were done at an interval of 15 days. The primary outcomes were objective signs like best-corrected visual acuity (BCVA); ophthalmoscopic signs such as superficial hemorrhages, dot-blot hemorrhages, hard exudates, cotton wool spots, neovascularization disc, neovascularization elsewhere, and fibrovascular proliferation; subjective symptoms such as diminished vision, blurred vision, frequent changes in presbyopia glasses, perception of flashes of light, floaters, and problem for dark adaptation. The secondary outcomes were fasting blood sugar (FBS), postprandial blood sugar (PPBS), urine sugar, serum cholesterol, hemoglobin (Hb), glycosylated HbA1C, liver function test, and renal function test outcomes were assessed before and after the treatment. **Results:** Ninety participants were included in the analysis of the primary outcome (62 in the trial and 28 in the control group). The trial group provided better results which were statistically significant on dot-blot hemorrhages, superficial hemorrhages, hard exudates, BCVA, FBS, and serum cholesterol. Both the groups provided almost similar effects in PPBS, Hb, HbA1C, and urine sugar which were statistically insignificant. Adverse effects were not reported in any of the patient among either groups. **Conclusion:** Ayurvedic treatment protocol is safe and effective in DR.

Keywords: Ayurvedic treatment protocol, diabetic retinopathy, *Durvadi Ghrita*, *Marsha Nasya*, *Rasayana Yoga*, *Takra Dhara*

Introduction

Diabetic retinopathy (DR), the leading cause of visual disability in diabetics, is an important complication of diabetes mellitus (DM).[1-5] Typical DR fundus characteristics include microaneurysms, hard exudates, diabetic macular edema (DME), and new vessels (in proliferative DR [PDR]). The current treatment of DR includes strict control of systemic conditions, intravitreal injections, and laser photocoagulation.[6] Intravitreal injections are generally well tolerated but can cause vision-threatening complications such as endophthalmitis, retinal detachment, and/or retinal vasculitis.[7] Although laser photocoagulation is highly effective, there are chances of complications such as choroidal effusions, exudative retinal detachments, macular edema, visual field deficits, and

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Address for correspondence: Dr. V. Krishna Kumar, Regional Ayurveda Research Institute for Eye Diseases, INS-106, Sector-25, Indira Nagar, Lucknow - 226 016, Uttar Pradesh, India. E-mail: drkkempran@gmail.com

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night vision defects.[8] The average medical expenditure for treating DR per eye was nearly three times more for patients with significant visual loss (3/60) than for those with normal vision (6/12).[9] Considering the limitations of the current management, safe and effective ayurvedic treatments would be integrated with the existing ones as add-on therapy.

A description of *Timira* (a disease characterized by blurred vision) as a cause or complication of *Prameha* DM is there.[10] Thus, DR would be taken as *Madhumehajanya Timira.* Among trials conducted on DR in different Post Graduate centers of Ayurveda, most were on single procedures such as *Tarpana* (retention of medicated ghee over eyes) or single herbal medicines. As DR is chronic, involvement of *Dhatu* (tissues) is deep, and *Dosha Dushti* (morbidity of body humor) is more, reversing pathogenesis by single medicine or procedure is challenging. Thus, a protocol was designed to test the hypothesis whether the adopted protocol is effective in DR.

The protocol included a preparatory phase – *Dipana Pachana* (stomachic and digestant), *Koshta Shodhana* (mild therapeutic purgation), and *Shiro Virechana* (eliminative nasal medication) prescribed one after another. The treatment phase included *Marsha Nasya* (nasal medication) with *Durvadi Ghrita*, followed by *Takra Dhara* (pouring medicated buttermilk over the scalp) with *Siddha Takra*. *Pratimarsha Nasya* (nasal medication of mild dose) with *Durvadi Ghrita* was started along with *Takra Dhara* and continued for 3 months. *Rasayana Yoga* was started along with *Marsha Nasya* and continued with other procedures for 3 months.

Dipana pachana was intended to increase metabolism before intake of *Rasayana Yoga*. *Prameha* is a systemic disorder; to eliminate the vitiated *Doshas* from the body, *Koshta Shodhana* (a mild *Virechana*) is vital. Further retinal exudation and hemorrhagic features of DR simulates *Urdhwaga Raktapitta* (extravasations/exudation per supraclavicular parts) and its primary line of treatment is *Virechana.* Thus, it was adopted to reduce intraretinal extravasations/ exudation. *Shiro Virechana* was included for the expulsion of accumulated *Kapha* from *Urdhwaga Srotas* (microchannels). *Marsha* and *Pratimarsha Nasya* was added for ocular nourishment. *Durvadi Ghrita* is *Shamana* (*Dosha* pacifying) and *Brimhana* (nourishing). Hence, it not only arrests bleeding but also strengthens the retinal capillaries, helping reverse and prevent pathogenesis. *Takra Dhara* has *Urdhwaga Shodhana, Shothahara* (reducing edema), and *Rakta Sthambhana* (arresting bleeding) properties. *Rasayana yoga* was added to strengthen the *Rasayanidaurbalya* (fragile microvasculature in the retina), which is evident in DR The objective of the present study was to evaluate the clinical efficacy of the adopted treatment protocol in DR.

Materials and methods

Selection of patients

Hundred patients diagnosed with DR (based on the International Clinical Disease Severity Scale for DR)[11] were recruited from the outpatient department of *Shalakya Tantra* of a tertiary academic hospital in Western India. The process and algorithm of the black box design protocol are shown in Figure 1. The consensus for the set of medicines and procedures for the study was made by discussion among the authors and through telephonic discussion with subject experts with at least 10 years of clinical experience.

Inclusion criteria

The patients of either sex between 30 and 70 years with type 2 diabetes who are not on insulin, with or without visual disturbances, but with detectable ophthalmoscopic features of DR such as exudates and hemorrhages; those with fasting blood sugar (FBS) in the range 126–220 mg/dl or postprandial blood sugar (PPBS) in the range 180–300 mg/dl were included in the study.

Exclusion criteria

The patients with type-1 diabetes or type-2 diabetes taking insulin; those with high-risk DR requiring emergency intervention; those with media opacities like cataracts that interfere with ophthalmoscopic findings; those with ocular pathologies such as glaucoma, high myopia, hypertensive retinopathy, and DR associated with pregnancy; those with best-corrected visual acuity (BCVA) <6/60 and who was highly debilitating and not able to withstand treatment procedures were excluded from the study.

Screening methods

Selected patients were subjected to a through examination; findings were recorded in the specially designed case pro forma, including as per *Ayurveda* and conventional medical system parameters. The examinations carried out included BCVA using Snellen's chart and Jaegar's chart (for near vision), slit lamp examination for any gross pathology in the anterior segment, ocular pressure with Schiotz tonometry, fundus examination by direct ophthalmoscope, indirect ophthalmoscope, and color fundus photography for evidence of DR and optical coherence tomography for retina and macula thickness. Ayurvedic parameters like *Prakriti* (constitution) were assessed. Laboratory investigations included hemoglobin (Hb), total leukocyte count, differential leukocyte count, erythrocyte sedimentation rate, routine and microscopical examination of urine, biochemical examinations such as FBS, PPBS, serum cholesterol, glycosylated HbA1C, liver function test (LFT) like aspartate aminotransferase (AST), alanine aminotransferase, and renal function test (RFT) like serum urea and serum creatinine were carried out at clinical laboratory at baseline and the end of 3 months.

Research design

The study was a randomized, controlled, black box design clinical study. A simple randomization method with computer-generated random tables was used for the study (www.randomization.com). The sample size was 70 in the trial group and 30 in the control group. This was calculated; with inputs-power = 70%, effect size = 0.50. The allocation ratio

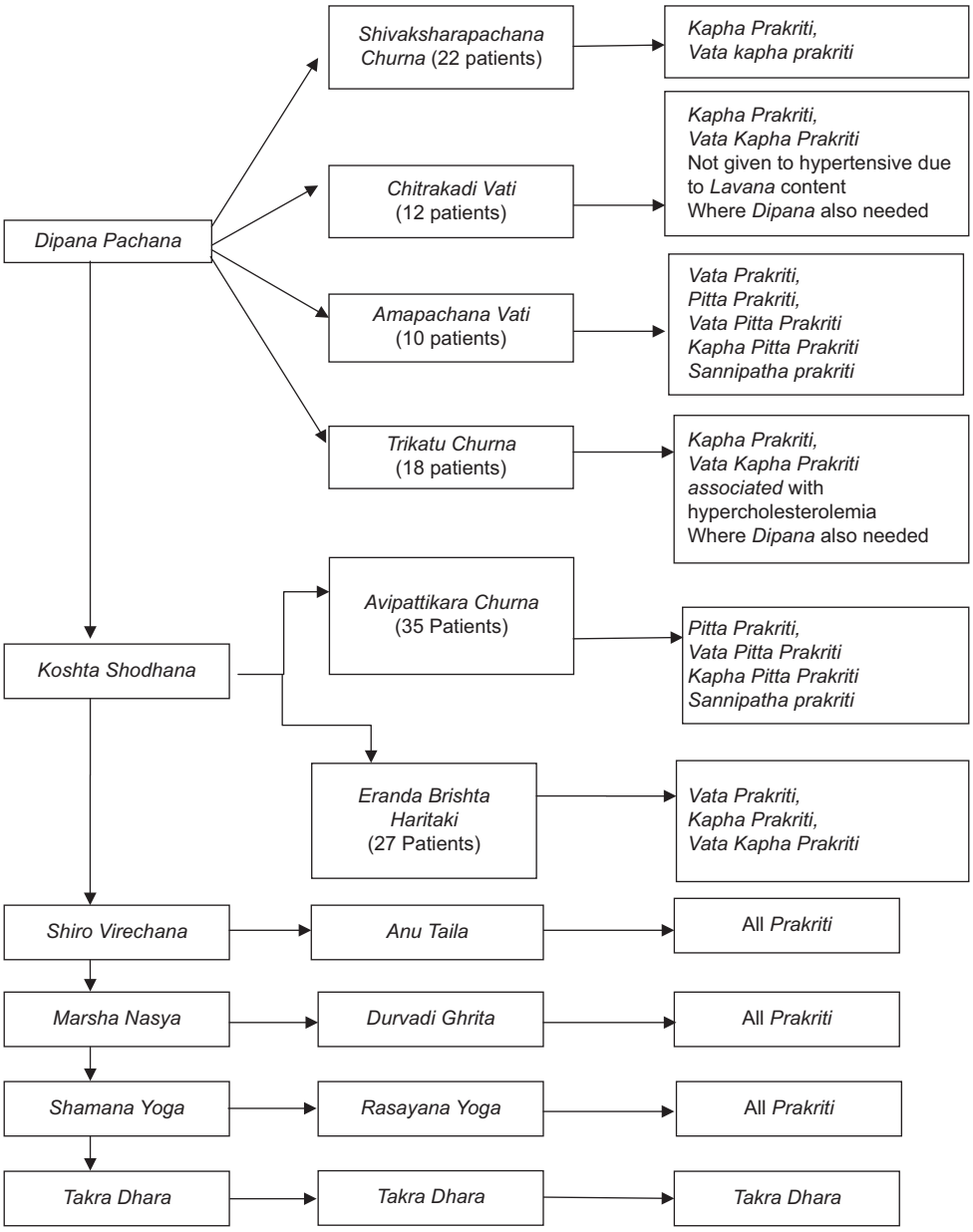

Figure 1: Depicting the process and algorithm of the black box design

was (70:30). The random allocation sequence was implemented through case record numbers. No significant changes were made to methods after trial commencement.

Intervention

All the patients were randomly divided into group A, the trial group, and group B, the control group. In group A, the preparatory phase (which is not included in the trial period) consisted of *Dipana Pachana*, *Koshtha Shodhana*, and *Shiro Virechana*. The treatment phase included *Marsha Nasya* and *Pratimarsha Nasya* with *Durvadi Ghrita*, *Takra Dhara* with *Siddha Takra* [Table 1], and internal administration of *Rasayana Yoga.* [Table 2] Details of therapeutic intervention are given in Table 3 and the standard operating procedure of all procedures is depicted in Table 4. At the end of this treatment procedure, *Marsha nasya* for a further 7 days and *Takra dhara* for 15 days were repeated in the next 2 months. Two follow-ups were done at an interval of 15 days. [Table 3] In group B, patients were kept under conservative treatment and observed for the whole therapy period of 3 months.

Both groups continued with their treatment for diabetes and DR if any. All the medicines in the trial group except *Swarnamakshika Bhasma* (purchased from Dhootapapeshwar Pharmaceuticals, Mumbai, with Quality Analysis Certificate) were prepared in the Pharmacy of Gujarat Ayurved University, Jamnagar, Gujarat, India, as per standard procedures. The nature and design of the study were explained to the patients, and informed consent was obtained. Institutional Ethics Committee approved the study (No. PGT/7 A/Ethics/2015-16/2625 dated

December 11, 2015) and the study was registered under the Clinical Trial Registry of India (CTRI) with CTRI No. CTRI/2016/04/006803 dated April 7, 2016. Data was collected from April 2016 to September 2017. The trial was stopped after achievement of sample size. Patients were asked to adhere to the treatment protocol and report any adverse events. Any existing or new manifestations during the intervention that caused considerable distress were planned to screen for possible adverse events. Any patient who developed sight-threatening complications during treatment was withdrawn and refer planned to ophthalmologist of conventional medicine.

Table 1: Ingredients of *Siddha Takra*

Drug	Botanical name	Part used	Proportion
Musta	*Cyperu rotundus* Linn.	Dried rhizome	1 part
Amalaki	*Embilica officinalis* Gaertn.	Dried pericarp	1 part
Yashtimadhu	*Glyccrrhiza glabra* Linn.	Dried stem	1 part
Daruharidra	*Berberis aristata* DC.	Dried stem	1 part
Lodhra	*Symplocus racemosa* Roxb.	Dried stem bark	1 part
Vasa	*Adathoda vasica* Nees.	Dried stem leaves	1 part
Chandana	*Santalum album* Linn.	Dried heartwood	1 part
Utpala	*Nymphaea caerulea* Sav.	Dried flower	1 part

25 g of powder of the ingredients numbered 1-8 were added in 1 L of buttermilk and 1 L of water, mixed thoroughly, kept overnight, filtered in the morning, and used in the procedure of *Takra Dhara*

Table 2: Ingredients of *Rasayana Yoga*

Drug	Scientific/botanical name	Part used	Proportion
Haritaki	*Terminalia chebula* Retz.	Dried pericarp	1 part
Amalaki	*Embilica officinalis* Gaertn.	Dried pericarp	2 parts
Vibhitaka	*Terminalia bellerica* Roxb.	Dried pericarp	1 part
Haridra	*Curcuma longa* Linn.	Dried rhizome	1 part
Guduchi	*Tinospora cordifolia* (Thunb) Miers.	Dried stem	1 part
Musta	*Cyperus rotundus* Linn.	Dried rhizome	1 part
Yastimadhu	*Glycyrrhiza glabra* Linn.	Dried root	1 part
Vasa	*Adathoda vasica* Nees.	Dried leaves	1 part
Swarnamakshika	Calcined copper pyrite		0.041 part

Criteria for assessment

Primary Outcomes

The primary outcomes were objective signs like BCVA; ophthalmoscopic signs like superficial hemorrhages, dot-blot hemorrhages, hard exudates, cotton wool spots, neovascularization disc, neovascularization elsewhere, and fibrovascular proliferation; subjective symptoms such as diminished vision, blurred vision, frequent changes in presbyopia glasses, perception of flashes of light, floaters, and problem for dark adaptation. A specialized scoring pattern was adopted for symptoms. Outcomes were assessed before and after the treatment.

Secondary Outcomes

The secondary outcomes were FBS, PPBS, urine sugar, serum cholesterol, HB%, HbA1C, LFT, and RFT. Outcomes were assessed before and after the treatment. No changes were made to trial outcomes after the trial commenced.

Statistical methods

Results were assessed in terms of percentage relief and statistical evaluations. Statistical analysis was carried out using Sigma Stat 3.1 [SigmaStat for Windows Version 3.11 Copyright 2004 Systat software, Inc, San Jose, CA, USA]. Comparison of within groups at two points was analyzed by paired *t*-test for objective criteria and signed rank test for subjective criteria. Comparison between the groups was analyzed using unpaired *t*-test.

Results

A total of 100 patients participated in the study, and baseline characteristics are depicted in Table 5. Later,

Table 3: Therapeutic interventions adopted

Procedure	Medicine used	Duration	Posology
Dipana Pachana	*Shivaksharapachana churna* or *Chitrakadi vati* or *Amapachana vati* or *Trikatu churna* or	5-7 days, according to *Koshta* of the patient	5-10 g or one tablet with hot water twice daily before food
Koshta Shodhana	*Avipattikara Churna* Or *Eranda Brishta Haritaki*	Next 5 days	5-10 g with hot water at 6 am according to *Prakriti* and *Koshta*
Shiro Virechana	*Anu Taila*	Next 7 days	8-10 drops instilled in each nostril at 9 am
Marsha Nasya	*Durvadi Ghrita*	After *Shiro virechana*, a gap of 1 week was given, followed by *Marsha nasya* for 7 days	8-10 drops instilled in each nostril at 9 am
Takra Dhara	*Siddha Takra*	Next 15 days	30 min at 9 am
Shamana Yoga	*Rasayana Yoga*	Started along with *Marsha nasya* and was continued along with other procedures for 3 months	3 g of powder with 2 g of honey and 5 g of ghee at bedtime
Pratimarsha Nasya	*Durvadi Ghrita*	Started along with *Takra Dhara* and was continued for 3 months	Two drops instilled in each nostril at 5 pm

Table 4: Standard operating procedure of the procedures

Name of the procedure	Standard operating procedure
Shiro Virechana/Marsha Nasya	Preoperative procedure
	Prepare the patient for the procedure; give necessary instructions regarding the procedure
	Informed consent of the patient should be taken after the clear description of the procedure, its purpose and complications
	Materials required
	Lukewarm water-quantity sufficient
	Prescribed medicament: Quantity sufficient
	Instrument for giving local *Baspa Sweda* (sudation): 1 No.
	Clean and dry towel: 1 No.
	Gokarna made of silver/steel/*Panchalouha*: 1 No.
	15° slanting table: 1 No.
	The patient should be advised to satisfy the natural urges
	Check vitals and carry out examinations of nasal sinuses, oral cavity, and ears
	Main procedure
	Patient should be asked to wash his/her mouth and face with lukewarm water
	Eyes of the patient should be closed and covered with a clean cloth
	Abhyanga (oil massage) and *Bashpa Sweda* should be done on the scalp, face, ears, neck, and shoulder for 10-12 min
	Wipe off the sweat with a clean dry towel gently
	Patient should be asked to inhale *Dhooma* (medicated fumes) from ignited *Haridra Varti* through the nose
	Make the patient lie supine on a 15 degree slanting table with head at the lower end and with relaxed and extended limbs
	Sweda should be done over the face repeatedly with warm palms
	Head is to be tilted backwards so that the nostrils are directed towards the ceiling
	Take one part of the medicine in a *Gokarna* (4-5 drops) and warm it by placing in hot water
	Tip of the nose should be raised with middle finger of the left hand
	Close the left nostril with the ring finger of the left hand
	Continuously pour half of the medicine in the right nostril with right hand
	Patient should be asked to inhale the medicine slowly and deeply
	Close the right nostril with the index finger of left hand
	Continuously pour the remaining medicine in the left nostril with the right hand
	Patient should be inhaling the medicine slowly and deeply
	Massage should be done over ears, forehead, cheeks, neck, shoulders, palm, and soles
	Patient should be made to hawk mildly and spit out the sputum on both sides alternately
	Sweda should be repeatedly done in sitting posture till the medicine is completely expelled out
	Enquire regarding *Vaktra Shudhi,* i.e., there must be no taste of the medicine instilled
	Procedure should be repeated once or twice
	Patient should be asked to relax for 15 min by lying on the table
	Wipe off the sweat and oil with a clean dry towel
	Make patient inhale *Dhooma* from ignited *Haridra Varti* through the mouth
	Luke warm water gargling should be advised
	The total duration of the procedure should be around 45 min/day
	Postoperative procedure
	Rest-patient advised to take rest in the supine position for the next 15 min
	If the patient complaints of any symptoms as giddiness/headache/nausea then has to be managed accordingly
	Meal and diet restrictions specific to *Sneha Vidhi Snehapana* (internal oleation) is to be adopted
	Specific medications, if any-based on the symptoms that precipitate while or after instillation
Takra Dhara	Preoperative procedure
	Prepare the patient for procedure; give necessary instructions regarding the procedure. Materials required
	Dhara Yantra with stand: 1 No.
	Powder of the ingredients: 25 g
	Takra: 1 L
	Patient should be asked to satisfy natural urges
	Check vitals before the procedure
	Hair of the patient should be shaved/cut short (tied tightly and fixed on either side of the head in the case of females)

Contd...

Table 4: Contd...

Name of the procedure	Standard operating procedure
	Main procedure
	Patient should be made to sit comfortably on the table with legs well extended
	Therapist should take a position on either side of the patient
	Apply the prescribed lukewarm oil over the vertex
	The patient should be made to lay supine position. Place a small pillow under the neck
	Eyes are to be covered with cotton gauze and also tie gauze should be tied around the head above the ears
	Plug the ears with cotton pieces
	Position the patient so that the tip of the wick comes 6-8 cm above the mid portion of forehead
	Dhara vessel should be held little away from the head
	Takra should be poured into *Dhara* vessel
	Vessel should be brought above the forehead of the patient
	Direct the *Dhara* coming through wick into patient's forehead
	Adjust the size of wick so as to make the size of *Dhara* equal to the thickness of the small finger of the patient
	Maintain a continuous and steady stream so that the *Takra* will fall into patient's entire forehead without interruption
	The therapist on the right side of the patient shall hold and oscillate the vessel with moderate speed from one end of the forehead to the other with his right hand
	Maintain uniform rate of oscillations throughout the procedure
	The therapist on the left side shall do gentle massage over the patients scalp in frequent intervals with his right hand
	The *Takra* falling should be poured again into the vessel after collecting from the *Droni*
	The *Takra* should not be heated or reused
	Procedure can be continued up to 45-60 min
	Postoperative procedure
	Hold the *Dhara* vessel away from the patient's head
	Gauze and earplug should be removed
	Wipe off the head with a clean and dry towel
	The patient should be asked to take rest for 1 h
	Advise to take bath in lukewarm/medicated water, if indicated

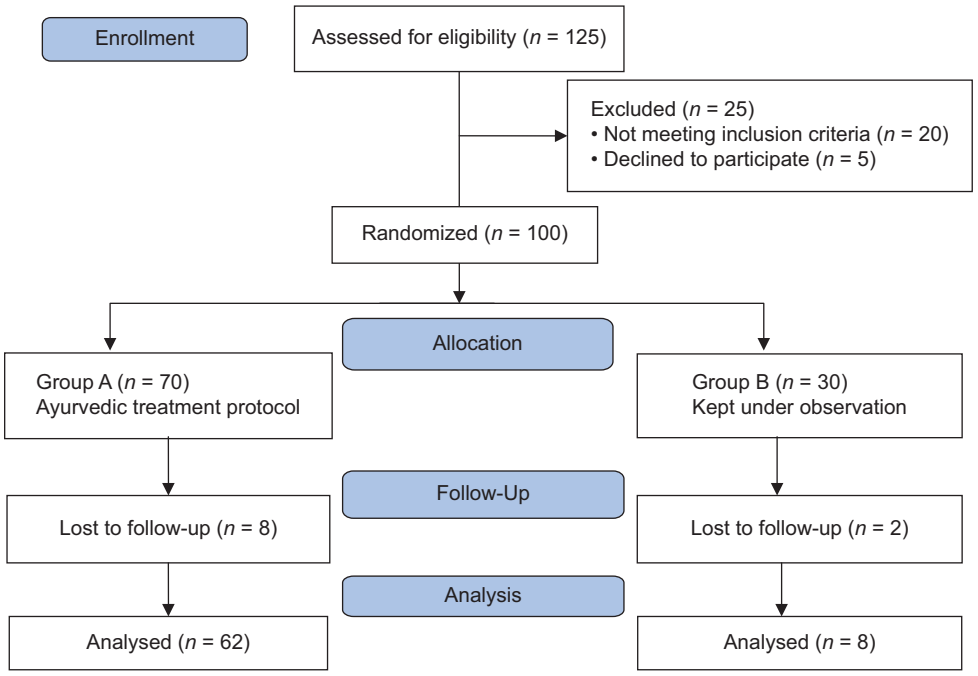

Figure 2: Participant flow chart

10 patients who dropped out were excluded from the study. [Figure 2] The incidence of sex in the groups shows a male preponderance (57%) compared to females (43%). Most were housewives (38%), followed by 25% retired. In dietary

etiological factors, 20% had excessive use of curd. 66% of patients were taking *Madhura Rasa* (sweet) dominant diet, and 55% were taking the *Snigdha Guna* (unctuous nature) dominant diet. It was observed that 63% of patients were of *Pitta Kapha Prakriti.* All (100%) patients had complaints of diminished vision, followed by 18% of patients having complaints of blurriness of vision. No patients complained of frequent changes in presbyopia glasses, perception of flashes of light, floaters, and dark adaptation problems. 95% of patients had nonproliferative DR (NPDR), 5% had PDR, and 4% had DME. A max of 73% had dot-blot hemorrhages. Superficial hemorrhages were seen in 49%. 60% of patients had hard exudates. Signs of PDR like neo vascularization disc and fibrovascular proliferation were few. 96% of patients had gradual onset of ocular complaints, and 4% had a sudden onset. A max of 48% had had a history of diabetes for up to 5 years, while 27% reported the onset of diabetes 6 to 10 years ago. 97% of patients had regular control of blood sugar levels. Positive family history was reported in 23%, and 77% had no family history of DM Furthermore, 41% were found to be hypertensive.

Table 5: Baseline characteristics

Characteristics	Trial group ($n=70$), n (%)	Control group ($n=30$), n (%)
Age (years)		
30-40	2 (2.85)	1 (3.33)
41-50	10 (14.28)	10 (33.33)
51-60	30 (42.85)	8 (26.66)
61-70	28 (40.00)	11 (36.66)
Sex		
Male	38 (54.28)	19 (63.33)
Female	32 (45.71)	11 (36.66)
Diagnosis		
NPDR	65 (92.85)	30 (100)
PDR	5 (7.14)	0
DME	3 (4.28)	1 (3.33)
Chronicity of diabetes (years)		
0-5	30 (42.85)	18 (60)
6-10	19 (27.14)	8 (26.66)
11-15	13 (18.57)	2 (6.66)
16-20	7 (10)	1 (3.33)
>20	1 (1.42)	1 (3.33)
Associated illness		
Hypertension	34 (48.57)	7 (23.33)
Hypercholesterolemia	2 (2.85)	0
Anemia	3 (4.28)	2 (6.66)
Family history of diabetes		
Positive	19 (27.14)	4 (13.33)
Negative	51 (72.85)	26 (86.66)

NPDR: Nonproliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, DME: Diabetic macular edema

Results

On symptoms such as defective vision and blurred vision, both groups had statistically insignificant results ($P > 0.05$). [Table 6] Treatment in group A was more effective in reducing dot-blot hemorrhages ($P < 0.05$), superficial hemorrhages ($P < 0.001$), hard exudates ($P < 0.05$), and change in BCVA ($P < 0.001$) [Tables 7-10] but on comparison statistically insignificant. [Table 11] On laboratory investigations like FBS ($P < 0.05$) and S. Cholesterol ($P < 0.05$), group A was better than group B and statistically significant, whereas, on PPBS, Hb, HbA1C, and urine sugar, both the groups were showing more or less identical results which were statistically insignificant ($P > 0.05$). [Tables 12 and 13]

Table 6: Comparative effects in both groups on subjective findings

Subjective findings	Group	n	Difference in means	Unpaired t-test			
				SD	SEM	t	P
Diminished vision	A	124	0.0726	0.260	0.0234	0.019	0.638
	B	56	0.0536	0.227	0.0304		
Blurred vision	A	22	0.167	0.381	0.0777	1.058	0.299
	B	6	0.000	0.000	0.000		

SD: Standard deviation, SE: Standard error, SEM: SE of the mean, t: t (paired t-test), P: Probability

Table 7: Effect of trial drugs on objective findings (right eye)

Objective findings	n	BT		AT		Difference	Percentage of difference	Paired t-test			
		Mean	SD	Mean	SD			SD	SEM	t	P
Dot-blot hemorrhages	46	1.76	0.84	1.56	0.91	0.19	11.11	0.40	0.05	3.30	0.002
Superficial hemorrhages	31	2.12	0.76	1.83	0.89	0.29	13.63	0.46	0.08	3.50	0.001
Hard exudates	34	1.76	0.89	1.61	0.77	0.14	8.33	0.35	0.06	2.38	0.023
Soft exudates	3	1.33	0.57	1.00	1.00	0.33	25.0	0.57	0.33	1.00	0.423
Macular edema	3	1.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	1.000
BCVA	62	2.40	1.68	2.17	1.73	0.22	9.39	0.52	0.06	3.38	0.001

BT: Before treatment, AT: After treatment, SD: Standard deviation, SEM: Standard error of the mean, BCVA: Best-corrected visual acuity, n S: Significant, HS: Highly Significant, t: t (paired t-test), P: Probability

Table 8: Effect of trial group on objective findings (left eye)

Objective findings	BT		AT		Difference	Percentage of difference	Paired *t*-test				
	Mean	SD	Mean	SD			*n*	SD	SEM	*t*	*P*
Dot-blot hemorrhages	1.76	0.82	1.59	0.85	0.16	9.459	42	0.37	0.05	2.86	0.007
Superficial hemorrhages	1.96	0.85	1.73	0.90	0.23	11.86	30	0.43	0.07	2.97	0.006
Hard exudates	1.74	0.89	1.64	0.75	0.96	05.55	31	0.30	0.05	1.79	0.083
Soft exudates	1.33	0.57	1.00	1.00	0.33	25.00	03	0.57	0.33	1.00	0.423
Macular edema	1.00	0.00	1.00	0.00	0.00	0.00	03	0.00	0.00	0.00	1.000
BCVA	2.64	1.76	2.40	1.83	0.24	9.14	62	0.53	0.06	3.57	<0.001

BT: Before treatment, AT: After treatment, SD: Standard deviation, SEM: Standard error of the mean, BCVA: Best-corrected visual acuity, *t*: *t* (paired *t*-test), *P*: Probability

Table 9: Effect of the control group on objective findings (right eye)

Objective findings	BT		AT		Difference	Percentage of difference	Paired *t*-test				
	Mean	SD	Mean	SD			*n*	SD	SEM	*t*	*P*
Dot-blot hemorrhages	1.47	0.77	1.42	0.69	0.05	3.57	19	0.22	0.52	1.00	0.331
Superficial hemorrhages	1.83	0.98	1.83	0.98	0.00	0.00	06	0.00	0.00	0.00	1.000
Hard exudates	1.37	0.80	1.31	0.60	0.06	4.54	16	0.25	0.06	1.00	0.333
Venous tortuosity	1.00	0.00	1.00	0.00	0.00	0.00	03	0.00	0.00	0.00	1.000
BCVA	1.78	1.66	1.71	1.58	0.07	4.00	28	0.66	0.12	0.57	0.573

BT: Before treatment, AT: After treatment, SD: Standard deviation, SEM: Standard error of the mean, BCVA: Best-corrected visual acuity, *t*: *t* (paired *t*-test), *P*: Probability

Table 10: Effect of the control group on objective findings (left eye)

Objective findings	BT		AT		Difference	Percentage of difference	Paired *t*-test				
	Mean	SD	Mean	SD			*n*	SD	SEM	*t*	*P*
Dot-blot hemorrhages	1.60	0.82	1.53	0.74	0.66	4.16	15	0.25	0.06	1.00	0.334
Superficial hemorrhages	2.00	1.00	2.00	1.00	0.00	0.00	05	0.000	0.00	0.00	1.000
Hard exudates	1.43	0.81	1.37	0.61	0.06	4.34	16	0.25	0.06	1.00	0.333
Venous tortuosity	1.00	0.00	1.00	0.00	0.00	0.00	03	0.00	0.00	1.00	1.000
BCVA	1.46	1.42	1.50	1.40	−0.03	−2.43	28	0.50	0.09	−0.37	0.713

BT: Before treatment, AT: After treatment, SD: Standard deviation, SEM: Standard error of the mean, BCVA: Best-corrected visual acuity, *t*: *t* (paired *t*-test), *P*: Probability

Table 11: Comparative effects in both groups on objective findings

Objective findings	Group	*n*	Difference in means	Unpaired *t*-test				
				SD	SEM	*t*	*P*	Significance
Dot-blot hemorrhages	A	88	0.182	0.388	0.0414	1.724	0.087	NS
	B	34	0.058	0.239	0.41			
Superficial hemorrhages	A	61	0.262	0.444	0.056	1.95	0.055	NS
	B	11	0	0	0			
Hard exudates	A	66	0.121	0.329	0.040	0.895	0.373	NS
	B	32	0.062	0.246	0.043			
BCVA	A	124	0.234	0.527	0.047	2.454	0.015	NS
	B	56	0.017	0.587	0.078			

SD: Standard deviation, SEM: Standard error of the mean, BCVA: Best-corrected visual acuity, NS: Not significant, *t*: *t* (paired *t*-test), *P*: Probability

However, in comparison, there was no statistical significance in any of the lab parameters except FBS. [Table 14] There was no statistically significant change in AST, ALT, urea, and serum creatinine in the trial group ($P > 0.05$) after taking *Rasayana Yoga*. In the trial group, out of 62 patients, 4 (06.45%) got moderate improvement after the completion of treatment, 23 (37.09%) got mild improvement, and 35 (56.45%) remained unchanged. No eye showed progression. In group B, out of

Table 12: Effect of the trial group on laboratory findings

Laboratory findings	BT		AT		Difference	Percentage of difference	Paired *t*-test				
	Mean	SD	Mean	SD			*n*	SD	SEM	*t*	*P*
FBS	133.06	46.88	164.09	50.32	−31.0	−23.3	32	51.90	9.17	−3.3	0.002
PPBS	184.73	74.52	187.33	62.49	−2.60	−1.40	30	67.95	12.4	−0.21	0.835
HbA1C	7.56	1.60	7.62	1.69	−0.08	−1.09	26	1.8	0.35	−0.23	0.617
Urine sugar	1.07	1.26	1.50	1.28	−0.42	−40	14	1.74	0.46	−0.92	0.374
Hb	12.34	1.45	12.41	1.43	−0.07	−0.56	30	0.69	0.12	−0.65	0.577
Serum cholesterol	171.25	47.43	189.48	47.65	−18.2	−10.6	31	31.09	5.58	−3.26	0.003
AST	25.93	10.65	24.90	7.85	1.03	3.98	31	11.38	2.04	0.50	0.617
ALT	20.06	8.14	21.51	8.21	−1.45	−7.23	31	9.33	1.67	−0.86	0.393
Urea	29.87	8.88	31.74	7.86	−1.87	−6.26	31	7.76	1.39	−1.34	0.190
Serum creatinine	1.20	0.48	1.18	0.39	0.01	1.60	31	0.44	0.08	0.24	0.811

BT: Before treatment, AT: After treatment, SD: Standard deviation, SEM: Standard error of the mean, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, *t*: *t* (paired *t*-test), *P*: Probability

Table 13: Effect of control group on laboratory findings

Laboratory findings	BT		AT		Difference	Percentage of difference	Paired *t*-test				
	Mean	SD	Mean	SD			*n*	SD	SEM	*t*	*P*
FBS	178.3	63.75	171.8	79.47	6.5	3.65	19	72.4	16.6	0.39	0.699
PPBS	210.3	83.69	223.3	67.36	−13	−6.18	17	84.7	20.5	−0.6	0.536
HbA1C	7.79	1.60	7.56	1.69	0.2	2.92	18	1.62	0.38	0.59	0.560
Urine sugar	1.66	1.37	1.25	1.42	0.41	25.0	12	1.16	0.33	1.23	0.241
Hb	13.25	1.78	13.22	1.52	0.0	0.27	19	1.50	0.34	0.10	0.916
Serum cholesterol	155.8	28.92	169.4	32.60	−13.5	−8.67	19	25.18	5.77	−2.3	0.031
AST	25.73	5.60	24.73	4.96	1.00	3.88	19	8.08	1.85	0.53	0.596
ALT	20.26	5.37	17.73	4.50	2.52	12.46	19	5.94	1.36	1.85	0.081
Urea	33.10	11.02	34.47	17.42	−1.36	−4.13	19	14.24	3.27	−0.4	0.681
Serum creatinine	1.09	0.31	1.27	0.29	−0.18	−16.8	19	0.31	0.07	−2.5	0.020

BT: Before treatment, AT: After treatment, SD: Standard deviation, SEM: Standard error of the mean, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, *t*: *t* (paired *t*-test), *P*: Probability

28 patients, 2 (07.14%) got moderate improvement after the completion of treatment, 6 (21.42%) got mild improvement, 18 (64.28%) remained unchanged, and 2 (7.14%) showed worsening in condition. No patients in either group reported any adverse effects. During the follow-up period, the condition of the patients in the trial group remained stable or improved, while that in the control group showed some progression, which was assessed by subjective criteria like diminished vision, etc.

Discussion

A recent systematic review predicted that there would be 103.12 million persons with DR, 28.54 million with vision-threatening DR (VTDR), and 18.83 million with clinically significant macular edema (CSME). in 2020 based on a global prevalence of 22.27% for DR, 6.17% for VTDR, and 4.07% for CSME The number of persons with DR, VTDR, and CSME is anticipated to climb to 160.50 million, 44.82 million, and 28.61 million, respectively, in 2045.[12] It is the need of the hour to search for an effective alternative approach through Ayurvedic treatment to preserve the eyesight of diabetic patients worldwide and improve their quality of life. The Ayurvedic approach differs from other contemporary systems in its holistic approach-which encompasses systemic and local purificatory/preparative procedures followed by the administration of target-specific medicines. In the case of DR, these include drugs that act on microangiopathies and correct the health of capillaries. They also help establish the normalcy of the altered blood-retinal barrier reducing the edema. The judicious use of detoxification procedures in Ayurveda such as *Koshta Shodhana* and *Nasya* checks the bleeding from the retina and revitalizes the retina reducing the chances of recurrence. Keeping all these facts, we designed a protocol. As per knowledge, this is the first study done as a protocol in treating DR.

Other studies in India[13] have also shown that men are at greater risk for DR, and we have made a similar observation. Maximum patients (51%) were uneducated, which shows their unawareness of health status and regular eye check-ups following the detection of DM This study's patients belonging to the middle class were higher (47%). It is noteworthy that previous studies have also shown the prevalence of diabetes to be higher in the middle-income group (12.4%) compared to lower socioeconomic strata[14] (6.5%). Regarding occupational

Table 14: Comparative effects in both groups on laboratory findings

Laboratory findings	Group	*n*	Difference in means	Unpaired *t*-test				
				SD	SEM	*t*	*P*	Significance
FBS	A	32	−31.03	51.90	9.176	−2.15	0.036	Significant
	B	19	6.526	72.43	16.61			
PPBS	A	30	−2.6	67.95	12.40	0.46	0.647	NS
	B	17	−13.0	84.72	20.54			
HbA1C	A	26	−0.08	1.8	0.353	−0.58	0.562	NS
	B	18	0.228	1.62	0.383			
Urine sugar	A	14	−0.429	1.742	0.465	−1.428	0.166	NS
	B	12	0.417	1.165	0.336			
Hb	A	30	−0.07	0.697	0.124	−0.33	0.736	NS
	B	19	0.036	1.509	0.346			
Serum cholesterol	A	31	−18.22	31.09	5.58	−0.55	0.581	NS
	B	19	−13.52	25.18	5.77			
AST	A	31	1.032	11.38	2.044	0.010	0.991	NS
	B	19	1.000	8.083	1.854			
ALT	A	31	−1.45	9.334	1.676	−1.65	0.104	NS
	B	19	2.526	5.948	1.364			
Urea	A	31	−1.871	7.766	1.395	−0.161	0.872	NS
	B	19	−1.368	14.27	3.275			
Serum creatinine	A	31	0.019	0.446	0.080	1.741	0.088	NS
	B	19	−0.184	0.313	0.071			

SD: Standard deviation, SEM: Standard error of the mean, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, NS: Not significant, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, *t*: *t* (paired *t*-test), *P*: Probability

history, maximum patients being housewives and retired ones shows the association of sedentary lifestyles and lack of exercise with DR *Avyayama* (lack of exercise) is the cause for *Santarpanajanya Vikaras* (diseases due to overnutrition) which include *Prameha*.[15]

Dietary *Nidana* such as *Madhura Guna* and *Snigdha Guna* dominant diet and intake of curd will lead to *Kapha Pitta Prakopa* (aggravation) and further add to the disease process. As observed, *Pitta Kapha Prakriti* is at maximum risk of *Kapha Pitta Dosha* being afflicted as *Kapha* and *Pitta* are more involved in the disease pathogenesis. We had maximum patients in the NPDR stage, which may be because the prevalence of NPDR is higher than other stages of DR.[16] Since maximum patients were in the stage of NPDR, signs of NPDR like dot-blot hemorrhages and hard exudates were present in large proportion. Signs of PDR like neo vascularization disc and fibrovascular proliferation were few. In 48% of patients, the onset of diabetes was within 5 years, and it seems a little contradictory as the studies conducted show that the occurrence of retinopathy symptoms mainly after 5 years.[17] Thus, the history of duration of DM is of detection of hyperglycemia; rather than actual occurrence. Most (96%) of patients having a gradual onset of ocular symptoms indicate the chronicity and severity of the disease by slow progression. That is why diabetes is said to be a slow and insidious killer. Furthermore, the sudden onset of symptoms occurs in a retinopathy patient in its proliferative stage.

Observation of 41% of patients being hypertensive shows the relation between hypertension and the incidence of DR Hypertension is an additive risk factor for the development of DR Increased blood pressure has been hypothesized, through the effects of increased sheer stress of blood flow, to damage the retinal capillary endothelial cells in the eyes of people with diabetes. The possible mechanisms by which hypertension may affect DR are hemodynamic (impaired autoregulation and hyperperfusion) and through vascular endothelial growth factor (VEGF). This hypothesis has been supported by observations from clinical studies, which showed an association between hypertension and the presence and severity of retinopathy.[18]

The line of management in *Timira* includes *Snehana* (therapeutic oleation), *Rakta Mokshana* (therapeutic blood-letting), *Virechana* (therapeutic purgation), *Nasya, Anjana* (collyrium), *Shiro Basti* (retention of medicated oil over scalp), *Basti* (therapeutic enema), *Tarpana, Lepa* (medicated paste), and *Seka* (ocular irrigation) that are to be followed repeatedly[19] of which *Snehana*, *Virechana (Koshta shodhana* and *Shiro Virechana), Nasya, Pratimarsha Nasya,* and *Takra Dhara* were followed in this trial because of their suitability. *Snehana* was done by administering *Rasayana Yoga* along ghee. *Dipana Pachana* increases metabolic activity and helps to digest/assimilate and excrete the metabolic waste accumulated in the tissue and system, thereby clearing the *Srotas* (microcirculation channels). *Shivkshara Pachana Churna*[20] and *Amapachana vati* were selected because of their *Amapachana* (digestion of undigested metabolic waste) property. *Trikatu Churna*[21] was used for *Dipana Pachana* as indicated in *Prameha* by Acharya Sushruta. *Chitrakadi Vati* was selected as it is both *Amapachana* and *Dipana*.[22]

Koshta Shodhana expels out accumulated *Kleda* (moisture) from the body, which possibly helps in the reduction of retinal and macular edema. Moreover, as the features of *Madhumehajanya Timira* are similar to *Urdhwaga Raktapitta* (bleeding through upper orifices)*; Koshta* Shodhana was used as *Pratilomahara Chikitsa*.[23] *Koshta shodhana* was done with *Eranda Bhrishta Haritaki* and *Avipattikara Churna*.[24] *Eranda Bhrishta Haritaki* was selected as it has *Vata Shamana* property. *Avipattikara Churna* was selected as indicated in *Prameha.*

Nasyayogas are also described for *Timira* because the nose is a gateway to drug administration in *Urdhwajatrugataroga* (diseases above the clavicle). *Acharyas* have recommended all efforts to strengthen the eyes by resorting to *Nasya, Anjana* in *Timira Chikitsa*.[25] Moreover, for diseases like *Raktapitta*, *Nasya* is a promising treatment modality. Hence, *Marsha Nasya* was selected for the trial. But before its administration, *Shiro Virechana* was done with *Anu Taila*[26] for local *Shodhana* and *Kapha Nirharana* (elimination of *Kapha*), considering *Kapha* predominance in the early retinopathy stages. *Pratimarsha Nasya* follows *Marsha nasya* as it strengthens sense organs and prevents further chances of occlusion of *Srotas*. Here, *Durvadi Ghrita*[27] was selected as it is indicated in *Raktapitta*. The contents are mostly *Sheeta Veerya* (cold in potency)*, Pitta Shamana* (pacifying)*, Rakta Prasadana* (blood purifying), and they have an anabolic effect that nourishes the *Dhatu.*

Takra Dhara has been widely practiced in Southern parts of our country, especially Kerala, in various ocular disorders, mainly in systemic pathologies like DR The direct reference is found in the book *Sahasrayoga* in which it is said to relieve debility, provide strength to the eyes, and induce sleep.[28] Due to its soothing and coolant effect, it not only checks bleeding but also relaxes the brain and helps relieve stress. *Takra Dhara* is said to be effective in both *Prameha* and *Urdhwanga Roga.* Most of the contents have either *Kashaya* (astringent) or *Tikta Rasa* (bitter), and *Laghu-Ruksha Guna* (light and dry). All drugs except *Daruharidra (Berberis aristata* DC.) are having *Sheeta Veerya*. These are the preferred pharmacological properties for the hemostatic, blood purifying, and coolant actions. Drugs present in *Siddha Takra* such as *Chandana (Santalum album* Linn.*), Vasa (Adathoda vasica* Nees.*) Utpala (Nymphaea caerulea* Sav.), and *Lodhra (Symplocus racemosa* Roxb.*)* have hemostatic properties.[29-32]

The treatment approach for a systemic illness like DR could not be holistic without *Rasayana* (rejuvenating) therapy, which has both curative and preventive parts. Here, a formulation of nine classically referred *Rasayana* drugs was selected, which are, *Pramehahara* (reducing blood sugar), *Medohara* (reducing fat)*, Raktavahasrotodushtihara* (correcting morbidity in vascular microchannels)*, Vatanuloma* (correcting the movement of *Vata*)*, Sophahara* (reducing edema) and *Chakshushya* (congenial to eyes). Angiogenesis, the key to diabetic blindness, which is regulated by VEGF's factor, was also kept in mind; hence the drugs having the anti-VEGF's property were also considered. Plants rich with polyphenols, terpenes, flavonoids, linoleic acid, and selenium are found to regulate or inhibit VEGF's property. *Triphala*[33] (*Terminalia chebula* Retz.*, Embilica officinalis* Gaertn.*, Terminalia bellerica* Roxb), and *Guduchi*[34] (*Tinospora cordifolia* [Thunb] Miers) have these properties.

In comparing two groups for defective vision and blurred vision, the difference in the means was insignificant, and there was no statistically significant change in symptoms like defective vision and blurred vision in both groups. The trial group effectively reduced dot-blot and superficial hemorrhages, which may be due to improving the health of retinal vasculature in this short duration of treatment. By *Rasayana yoga, Takra Dhara,* and *Nasya,* the *Rasayani Daurbalya* is countered; thereby, the structural health of the vasculature is strengthened. That is why no fresh hemorrhage was observed.

The trial group was more effective and statistically significant in lowering FBS and serum cholesterol, showing that the integrated approach in DM gives a better FBS and serum cholesterol control. It reflects that treatment by *Rasayana* therapy after *Koshta shodhana* in the trial group was helpful in blood sugar and S. Cholesterol control and its maintenance for an extended period. The reduction in FBS may be attributed to the *Pramehahara* property of *Haritak*i (*Terminalia chebula* Retz.*) Amalaki* (*Embilica officinalis* Gaertn.), *Haridra (Curcuma Longa* Linn.*)*, and *Swarnamakshika Bhasma* (calcined copper pyrite) in *Rasayana Yoga*.[35-38] The trial group showed no statistically significant change in AST, ALT, urea, and serum creatinine. Thus, there was no change in LFT and RFT in patients of the trial group after taking *Rasayana yoga*. All patients reported improving their physical and mental well-being, which suggests that the protocol improves the quality of life and vision. Some reported good sleep following *Takra dhara*, which verifies its soothing and mentally relaxing effect.

The limitation of our study was the small sample size, the data analysis was not performed as per the standard of a black box design, the black box design was adopted only for *Dipana Pachana* and *Koshta Shodhana* and not for other components of the protocol due to feasibility issues. The protocol with a black box design in each treatment component should be tried for a long duration and with more sample sizes having additional criteria for assessment of the quality of vision and quality of life. Assessment of general ocular health with regard to diabetic ophthalmopathy in addition to retinopathy would also be done.

Conclusion

The trial group where Ayurvedic treatment was also given with a modern counterpart showed an overall better effect. It has helped to break the pathogenesis and arrest the progression of the disease as it is evident from the study that no eyes showed progression after treatment in the trial group, whereas the other group showed some percent of worsening also. The better

results in the trial group may be due to the improved health status of whole-body vasculature, especially microvasculature in the retina, which prevented further exudations and hemorrhages. *Rasayana Yoga* is safe as there was no change in liver function and RFT in patients of the trial group after its intake. This study emphasizes the importance of an integrated approach in healthcare. Considering the merits of Ayurvedic approaches, there is a need for collaborative research to generate evidence at a larger scale in treating DR.

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Conflicts of interest

There are no conflicts of interest.

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