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Original Research Article (Clinical)

A double-blind controlled clinical trial to evaluate the effects of nasal therapy with *Vrihatajivakadya* oil on different viscosities in patients with migraine

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ABSTRACT

Background: Migraine, characterized by pain of a specific type in one half of the head has a close resemblance with *Ardhavabhedaka* described in Ayurveda. *Nasya karma* (nasal therapy) with *Vrihatajivakadya* oil is indicated in *Ardhavabhedaka*. Low viscosity oil (LVO) and medium viscosity oil (MVO) prepared by *Snehapaka* (a specific Ayurveda method for preparation of oil) are advocated in different classical *Ayurveda* texts for *N. karma*.

The objectives: This study was done to assess the effects of *Vrihatajivakadhya* oil on different viscosities in *N. karma* for the better *Ayurveda* management of migraine.

Material and methods: In this double-blind randomized controlled trial a total of 90 patients were randomly divided into two groups for *N. karma with* oil of different viscosities. In the group treated with LVO, 44 patients completed their treatment and one patient was lost in follow-up. In another group treated with MVO, 45 patients were enrolled and completed the intervention. *N. karma* was done with this oil in the dose of 6 drops per nostril for the duration of 14 days for each participant. The follow-up was done on the 15th day and 45th days. The assessment was done by the Migraine Disability Assessment Score (MIDAS) and Migraine Specific Quality of Life Assessment scale.

Result: During the trial, significant improvement in both the groups on both parameters was observed. No adverse event was noticed during the study.

Conclusion: N. karma with MVO had better improvement. No adverse event was noticed during the study. *N. karma* with these oils is effective and safe for migraine.

1. Introduction

Migraine is a genetically influenced, multifactorial, disabling, and recurrent, hereditary neurovascular disorder characterized by episodes of moderate-to-severe headache. It is often unilateral and generally associated with nausea, and increased sensitivity to light and sound [1].

Migraine without aura is the most common type (75% of cases). It can be considered in Ayurveda as *Ardhavabhedaka* (~migraine); a *Shiroroga* (disease of the head region) characterized by pain of a specific type in one half of the head [2]. Ayurveda emphasizes that if this condition is left untreated for a prolonged time it can cause the destruction of the eyes and ears [3]. The prevalence of the disorder in American Indians is 18.4 percent and mostly affected those are of aged 18–44 years [4]. Prevalence of migraine in India is 14.12% and is more common in women, than men [5]. Irregular lifestyle, environmental factors, and stress play a major role in migraine onset. Present-day lifestyle, personal behaviors, and socio-cultural influences contribute to the derangement of *Tridoshas* (~three-body humor) [6].

Nowadays, various conservative treatment modalities including various pain killers are adopted for migraine. These managements are not alone sufficient and have lots of contraindications. The multifaceted management of migraine has a high risk for side

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effects. In Ayurveda *Nasya karma* (nasal therapy) is widely used for Migraine. Few evidence-based studies are also published to ascertain the effect of *N. karma* on migraine. Two types of a medicated oil having different viscosity, prepared by Ayurveda-specific procedures are indicated for *Nasya Karma* in classical texts. These are prepared by *Mridu* (mild) *Snehapaka* (specific Ayurveda method for preparation of oil) or *Madhyama* (moderate) *Snehapaka*. *Charaka* indicated lesser viscosity oil (LVO) for *N. karma* while *Shushruta* advocated for medium viscosity oil (MVO) for *N. karma* [7]. Here query arises that which version is more useful for clinical practices. Considering these facts present work was designed with the primary aim of studying the comparative efficacy of *N. karma by* LVO and MVO of *Vrihatjivakadya* oil [8] in the management of Migraine. In this study, we also evaluated the safety of Nasya *karma* with these oils in the management of migraine.

2. Methods

2.1. Study design and oversight

This was a double-blind randomized control parallel-group study. Randomization was done by computer-generated randomization sequence and treatment allocation was carried out using concealed envelopes. The second author generated a randomization list. The list was not accessible to anyone else. The trial was registered at the clinical trial registry of India under CTRI/2018/10/016140 and was approved by the institutional ethics committee (IEC/ACA/2018/23). Written informed consent forms were provided by participants and from parents or guardians in case of the minor participant before taking part and they were not reimbursed for participation. Participants were recruited by the first author at O.P.D. and I.P.D. of the National Institute of Ayurveda hospital Jaipur placed patients in trial by computer-generated randomization sequence in consultation with the second author and provides investigational drugs for *Panchakarma* therapy. *N. karma* of these participants was done by qualified professionals who were blinded with the interventional drug. The third author assessed these participants independently during treatment and follow-up duration. All the authors were blinded with the *Snehapaka*/concentration of interventional drug till the completion of this trial. Information regarding the concentration of drugs for these two groups was obtained from the fourth author after the completion of the trial at the time of data interpretation. Participants were also blinded to the interventional drug.

2.2. Sample size and its estimation

Due to the absence of any baseline data, we assumed that *N. karma* with MVO would impart 50% more relief than LVO. We assumed the standard deviation (SD) of 1.18 from a similar published study on *N. karma* [9]. A sample size of 47 participants is needed per group with 5% type 1 error and 80% power. We adjusted the sample size to 50 participants in each group.

Initially, participation of 100 participants was planned for the study but we were able to recruit only 90 participants due to COVID-19 lockdown conditions at that time. Hence a total of 90 participants, diagnosed as having *Ardhavabhedaka* or migraine based on the International Classification for Headache Disorders, 3rd edition (ICHD-3) criteria (https://ichd-3.org), were placed in the following two groups by computer-generated randomization process. In administered group total of 45 participants were recruited out of them one participant was lost in follow up hence 44 participants were analyzed. In the MVO administered group total of 45 participants were recruited and analyzed [Fig. 1].

2.3. Participants

Participants of *Ardhavabhedaka* or migraine were pre-screened. The participants who fulfilled the inclusion criteria were randomly placed in two groups.

2.4. Inclusion criteria

Patients of either sex irrespective of their occupation, religion, and socio-economic status, between 8 and 80 years of age [10] with clinical signs and symptoms of Migraine without aura and fit for *Nasya Karma* were included in participation.

2.5. Exclusion criteria

Patients with severe systemic disorders such as Uncontrolled Hypertension, Cardiac problems, Diabetes Mellitus, Tuberculosis, Leprosy, Paralysis, and malignant disease were excluded. Patients suffering from sinusitis, hemiplegic migraine, basilar migraine, retinal migraine, status migrainosus, and headache due to any organic lesion or due to any chronic systemic disease were also excluded.

2.6. Intervention

2.6.1. Selection of drugs

LVO and MVO of *VrihatjivakadyaTaila* indicated in the management of *Ardhavabhedaka* were selected for *NasyaKarma* in the present study. The trial drug was prepared and provided with quality control by the GMP-certified Pharmacy of the institute. Viscosities of LVO and MVO were determined by a capillary viscometer. The viscosity measured for LVO was 86.93 mPa-s (millipascal-second) and 91.93 mPa-s for MVO. The density of these two oils was 0.9577 g/ml (grams per milliliter) and 0.9582 g/ml respectively. The specific gravity, refractive index, peroxide value, saponification value and acid value for LVO were 0.93545 g/ml,1.466,4.42,136.52 and 0.61 respectively and for MVO were 0.9359 g/ml,1.465,1.49,123.33 and 0.56 respectively. Test methods adopted for these parameters were according to Ayurvedic pharmacopeia of India Part-II volume IV 2017.

2.6.2. Trial intervention

Participants from both OPD and IPD were selected for *N. karma*. In one group LVO and in another group, MVO was instilled in the dose of 6 drops per nostril in the head low position with a slight elevation of the leg, once a day for 14 days. The average amount of six drops of this particular oil was 0.4 ml. *N. karma* was done before the meal and in *Purvahana* (before the afternoon) as indicated in classical text to avoid complications of this process. (3 chapter 9/98). Both *Abhyanga* (massage) and *Mridu Swedana* (~ mild sudation) of the head and neck region were done as preparatory measures. Installation of oils was followed by *Mridu Swedana*, medicated smoking with *Dashmoola Kwatha* (~ decoction of 10 Ayurveda plants) [11], and gargling with lukewarm water medicated with *Sudha tankan bhasma* (incineration of $Na_2B_4O_7.10H_2O$). [11 chapter 3/288] After *Nasya Karma,* every patient was asked to take a normal diet after 48 min of the procedure and advised to avoid loud speaking, an excessive vehicle travelling, excessive walking, excessive sitting, excessive untimely eating, an unwholesome diet, day napping, and sexual indulgence during the course of *Nasya Karma* and follow up. Standard operative procedures guidelines of the institute were adopted for *N. karma* intervention.

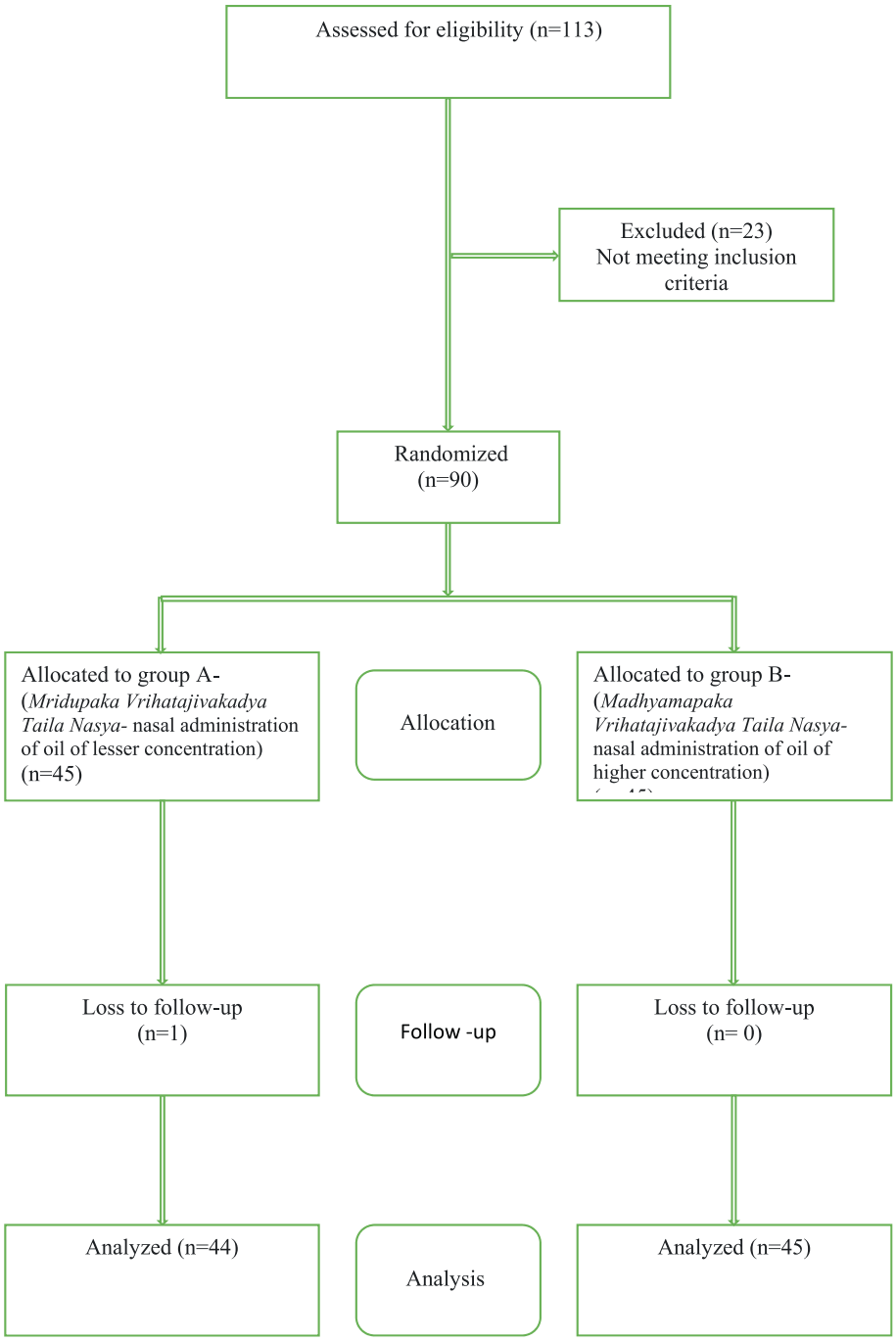

Fig. 1. Enrolment of patients.

2.7. Outcome measures

Changes in Migraine Disability Assessment Test (MIDAS) and Migraine Specific Quality of Life Assessment scale at baseline and 45th day of enrolment. Safety and any adverse effects were also measured.

2.8. Study duration and follow-up

Duration of treatment were 14 days for LVO and MVO administered groups. Patients were assessed on the baseline, 15th day, and 45th day of enrolment.

2.9. Statistical analysis

In this trial, results were obtained by using IBM Graph Pad version 26 software (assessed on 27 June 2020 at https://www.graphpad.com). Descriptive analysis was used to calculate the frequency and distribution of patients [Table 1]. All the descriptive data were analyzed to observe the homogeneity of groups for all the possible confounding factors. All outcome data were analyzed by intention -to- treat approach. Mann–Whitney Test was used to compare the difference between pre-and post-intervention values and the Wilcoxon matched-pairs signed rank test was used to compare the differences between the two groups for the same

Table 1
Details of Patient's profile.

S.No.	Clinical profile	Low Viscosity Oil	Medium Viscosity Oil	Total
1.	Mean Age + standard deviation	34.7 ± 9.2	34.8 ± 11.3	34.7 ± 10.2
2.	Sex			
	Male	14	12	26 (29.2%)
	Female	30	33	63 (70.8%)
3.	Religion			
	Hindu	37	36	73 (82%)
	Muslim	7	9	16 (18%)
4.	Educational status			
	Primary	1	3	4 (4.5%)
	Middle	11	8	19 (27.4%)
	Secondary	6	7	13 (14.5%)
	Higher secondary	11	13	24 (%)
	Graduate	15	13	28 (27%)
	Post Graduate	0	1	1 (1.1%)
5.	Occupation			
	Office work	11	5	16 (17.9%)
	House wife	20	25	45 (50.5%)
	Student	6	9	15 (16.8%)
	Self employed	5	6	11 (12.3%)
	labourer	2		2 (2.2%)
6.	Marital status			
	Married	39	34	73 (82%)
	Unmarried	5	11	16 (18%)
7.	Habitat			
	Rural	13	11	24 (26.9%)
	Urban	31	34	65 (73.1%)
8.	Socio economic status			
	Lower class	14	20	34 (38.2%)
	Middle class	21	18	39 (43.8%)
	Middle higher class	6	3	9 (10.1%)
	Higher class	3	4	7 (7.9%)
9.	Activity level			
	Sedentary	7	5	12 (13.5%)
	Mild physical activity	35	40	75 (84.3%)
	Moderate physical activity	2	0	2 (2.2%)
10.	Dietary history			
	Vegetarian	22	28	50 (56.2%)
	Mixed diet	22	17	39 (43.8%)
11.	Sleep pattern			
	Optimum sleep	15	17	32 (36%)
	Suboptimum sleep	12	15	27 (30.3%)
	Excessive sleep	5	4	9 (10.1%)
	Day nap	12	9	21 (23.6%)
12.	*Deha Prakriti*			
	Vata Pitta	21	19	40 (44.9%)
	Pitta Kapha	11	17	28 (31.5%)
	Vata Kapha	12	9	21 (23.6%)
13.	*Manasa Prakriti*			
	Sattva	8	7	15 (16.9%)
	Raja	17	18	35 (39.3%)
	Tama	19	20	39 (43.8%)
14.	*Sharir Sara*			
	Pravara	6	4	10 (11.2%)
	Madhyama	29	30	59 (66.2%)
	Avara	9	11	20 (22.4%)
15.	*Sharir Samhanana*			
	Pravara	9	10	19 (21.3%)
	Madhyam	32	34	66 (74.1%)
	Avara	3	1	4 (4.5%)
16.	*Satva*			
	Pravara	11	9	20 (22.5%)
	Madhyam	20	24	44 (49.4%)
	Avara	13	12	25 (28.1%)
17.	*Abhyavaharana shakti*			
	Pravara	10	8	18 (20.2%)
	Madhyam	22	26	48 (53.9%)
	Avara	12	11	23 (25.8%)
18.	*Kostha*			
	Mridu	9	12	21 (23.6%)
	Madhyam	24	21	45 (50.6%)
	Krura	11	12	23 (25.8%)
19.	*Agni*			
	Sama	13	16	29 (32.6%)
	Vishama	27	26	53 (59.6%)
	Tikshana	4	3	7 (7.9%)

Table 1 (*continued*)

S.No.	Clinical profile	Low Viscosity Oil	Medium Viscosity Oil	Total
20.	*Vyayama shakti*			
	Pravara	4	6	10 (11.2%)
	Madhyam	27	23	50 (56.2%)
	Avara	13	16	29 (32.6%)
21.	Distribution of headache Ardhavbhedaka			
	Throbbing	5	4	9 (10.1%)
	Cutting	11	13	24 (27%)
	Pricking	17	19	36 (44.4%)
	Pulsating	11	9	20 (22.5%)
22.	*Vaya*			
	Balyavastha	1	2	3 (3.4%)
	Yuvavastha	15	16	31 (34.8%)
	Madhyama	27	26	53 (59.6%)
	Vriddha	1	1	2 (2.2%)
23.	Comorbidities			
	Hypertension	1	0	1 (1.1%)
	Diabetes mellitus	0	1	1 (1.1%)
	Hypothyroidism	1	2	3 (3.4%)
24.	Treatment history			
	Allopathic	26	30	56 (62.9%)
	Ayurvedic	6	4	10 (11.2%)
	Allopathic + Ayurvedic	7	5	12 (13.5%)
	Allopathic + Homeopathic	2	1	3 (3.4%)
	None	3	5	8 (9%)
25.	*Samyaka Suddhi Lakshana* in *Nasya Karma*			
	Laghavama Shirasa	44	45	89 (100%)
	Suddhi Strotas	44	45	89 (100%)
	Vyadhi Nirjaya	44	45	89 (100%)
	Chitaindriya Prasadana	44	45	89 (100%)

outcome measures. All the statistical tests were interpreted as significant at a 5% level ($p < 0.05$).

3. Result

3.1. Study population

Participants' profiles are detailed in the table [Table 1]. The mean age of the patient was 34.7 (SD-10.2). One patient was lost in follow-up due to the lockdown condition in the COVID-19 crisis. Inthispresentclinicaltrialmaximumnumberofpatientsi.e.,68.9 % belongsto25-45agegroup with the majority of female subjects i.e., 70.8%, and the majority of them were housewives. A maximum number of the patient were *Vata Pitta Prakriti* (~body constitution)-44.9%, *Tamas Manas Prakriti* (~mental constitution) −43.8%, *Rakta Sara* (~ purest body tissue related with blood)-36.7%, *Madhyama Samhanana* (~ Sub optimum body built) −74.1%, *MadhyamaSatmya* (~sub optimum homologous)-38.9%, *MadhyamaSattva* (~sub optimum mental/spiritual strength) −49.4%, *MadhyamVyayamaShakti* (~ medium endurance)-56.2%, *MadhyamaAharaShakti* (~medium food intake) −53.9%, *MadhyamaJaranaShakti* (~ medium food intake)-55.6%, Vegetarian-55.5%, *Madhyama Kostha* (~ moderate bowel habits) −50.6%, *Vishamagni* (~oddity in digestive capacity) −59.6%, Majority of patients had a history of the day sleeping and night awakening, exposure to sunlight, *Chinta* (~Anxiety) and *Krodha* (~resentment), etc. 76.7% patients were addicted for tea. The majority of patients had chronicity between2-10years (64.4%), Site of headache (Frontal Region 43.3%), Repeated headache present (91.1%), and Pricking type headache (40%). In this study, no adverse events were observed throughout the trial in both groups. We had observed comorbidities in five participants and already prescribed medicines for these comorbidities were continued to these participants during the trial.

3.1.1. Effect of interventions

The clinical data presented here is based on the 89 patients of trial work. The effect of interventions is presented in table [Table 2]. Analysis of Pre and post-intervention showed significant relief ($p < 0.05$) of the migraine disability assessment test in group A (17.89 ± 11.42) and group B (18.69 ± 9.76). Analysis of Pre and post-intervention also showed significant relief ($p < 0.05$) in migraine-specific quality of life assessment in group A (30.57 ± 5.63) and group B (37.20 ± 5.55). More improvement was seen in group B in both parameters. The differences between the two groups were significant in the migraine disability assessment test with a p-value of 0.015 and in migraine-specific quality of life assessment with a p-value of 0.022. Better improvement in percentage in Group B for migraine Specific Quality of Life Assessment questionnaire was also noticed [Supplementary Table].

Table 2
Before and after comparison within two treatment arms expressed in mean and standard deviations (S.D.)−.

Variable	LVO group			MVO group			SD^a For LVO group	SD^a For MVO group
	Baseline	After treatment	Mean change (mean ± SD)	Baseline	After treatment	Mean change (mean ± SD)		
MIDAS	34.09	16.11	17.98 ± 11.42	33.11	14.42	18.69 ± 9.76	6.69	5.67
Migraine Specific Quality of Life Assessm-ent scale.	53.02	22.45	30.57 ± 5.63	53.44	16.24	37.20 ± 5.55	4.73	3.77

SD - Standard deviation, SD^a - Standard deviation of Inter group comparison., LVO- Lesser Viscosity Oil, MVO- Medium Viscosity Oil.

3.2. Safety and tolerability

CBC, ESR, FBS/RBS, serum creatinine, blood urea, SGOT, and SGPT were done at baseline and day 15 to assess the safety of the study. No abnormal laboratory results or adverse events were reported. In LVO significant changes are observed in Neutrophils (P = 0.438), Lymphocytes (P = 0.005) Monocytes (P = 0.036), and Fasting blood sugar (P = 0.000) while in MVO significant changes are observed in Haemoglobin (P = 0.034), Neutrophils (P = 0.014), Monocytes (P = 0.000) and serum creatinine (P = 0.033). All the parameters were in the normal range. There was no significant difference in these parameters in LVO and MVO [Table 3].

4. Discussion

This study was planned after assessing the *Samprapti* (pathology) of migraine which is similar to *Ardhavabhedaka* described in the classical text. Nasal therapy for *Ardhavabhedaka* management is most beneficial in migraine headaches as it directly influences the head region and is thus helpful in breaking the pathology of migraine. Nasal administration of the drug is widely practiced by Ayurveda physicians for migraine headaches. One similar study in biomedicine to develop lyophilized nasal inserts for migraine treatment has been published [12].In Ayurveda LVO and MVO both are advocated for nasal administration in *Ardhavabhedaka* by different scholars. A query arises for a better option among the oil of two variable viscosities. Hence, this study was carried out to ascertain a better formulation. A randomized double-blind study was planned to exclude any bias. Here, investigators and participants were blind to the viscosities of oils.

We had observed that *Nasya* with both LVO and MVO were effective in the management of migraine. But the effect was more in MVO. We had not noticed any episodes of migraine in any participants of this trial during the follow-up. LVO and MVO of *Vrihatjivakadya* oil were used for *N. karma* in this trial. *Jivaka* (*Crepidium acuminatum* (D.DON) SZLAC.), *Draksha* (*Vitis vinifera* L.), *Madhooka* (*Madhuca indica* GMEL.), *Bala (Sida cordifolia* L.), *Chandana* (*Pterocarpus santalinus* L.F.), *Vidari* (*Pueraria tuberosa* (ROXB. EX. WILLD.) DC.), goat flesh, milk, sesame oil etc. are the contents of *Vrihatjivakadya* oil which have anabolic, anti-inflammatory and pain stabilizing effects. This oil is also rich in protein, carbohydrates, lipids and other micronutrients and hence is nutritious in nature. *Vrihatjivakadya* oil is having *Vatanashaka* (~mitigation of vitiated *Vata dosha)*, *Kaphanashaka* (~mitigation of vitiated *Kapha dosha)*, *Sothanashaka* (~mitigation of inflammation), and *Vedanasthapaka* (pain stabilizing effect) properties and *Vrihatjivakadya* oil is also indicated in the treatment of *Ardhavabhedaka* [8].*Vata dosha* and *Kapha dosha* is mainly vitiated in *Ardhavabhedaka*. Vasodilation is the main pathophysiology of migraine and headache is the cardinal symptom of migraine. *Vataprakopa* (vitiation of *Vata dosha*) can lead to vasodilation. Uses of *Sneha* and *Swedana* (sudation therapy) can mitigate this *Prakupita vata* (vitiation of *Vata dosha*) and by this mechanism can relieve migraine. *Snehana* (oleation therapy) and *Swedana* are an integral part of *N. karma* as *Purva karma* (preparatory measures). *Swedana*, *Dhoompana* (medicated smoking), and *Kavala* (~washing of buccal cavity) are also used as *Paschata karma* (post-procedures measures). *Dhoompana* is helpful in the removal of slimy secretion from buccal and nasal cavities and *Kaval* is used for cleaning and restorative action of the buccal cavity. *Dashmool kwath* was used for medicated smoking through the nose as this is also indicated for nasal therapy in *Ardhavabhedaka*. Kaval was done with lukewarm water mixed with *Tankan bhasma* which is having the property of *Kaphanashana* (Pacifying the *Kapha dosha*/removal of slimy secretion from the nasal and buccal cavity).

Hormonal imbalances and metabolic disturbances are also etiological factors for migraine [13].Few studies have reported the beneficial effect of *N. karma* on above said etiological factors [9]. Some studies suggest that multiple primary neuronal impairments can lead to a series of extracranial and intracranial changes that cause migraines [14]. Due to nociceptor activation of the trigeminal system vasodilation, edema, and plasma protein extravasation occurs which leads to Neurogenic inflammation. It is also associated with the release of vasoactive neuropeptides like substance P, calcitonin gene-related peptide, and neurokinin a [15]. Neurons tend to become more responsive to stimulation due to this Neurogenic inflammation [16]. The formulation may reduce inflammation, plasma protein extravasation, activities of vasoactive neuropeptides, and neuron stimulation by its virtues-*Sothanashaka, Kaphanashaka, Vatanashaka,* and*Vedanasthapaka* respectively. Pre, main and post procedures of *Nasya Karma* may also relieve all these mechanisms and stimulants of the trigeminal system. Hence *Nasya Karma* with this oil was the choice for this clinical study. Uses of oleaginous products, oleaginous medicaments, and *Shirovirechana* (bio-purification of the head region by nasal therapy) are the main measures for the treatment of the *Ardhavabhedaka*. [3, verse 77] This was also the reason to select the *Nasya Karma* with oil for the present work.

Various factors can influence the efficiency of nasal delivery. It is dependent on physiochemical properties like molecular size, lipophilicity, pH, concentration, osmolarity, viscosity, enzymatic

Table 3
Biochemical parameters.

Details		LVO (N = 44)		MVO (N = 45)	
Test	Normal range	Baseline (mean ± SD)	Day 15 (mean ± SD)	Baseline (mean ± SD)	Day 15 (mean ± SD)
ESR	0–20 mm/h	14.75 ± 11.09	14.45 ± 6.18	13.29 ± 6.29	14.13 ± 4.52
Hb	Male-13 to 17 g/dl Female-11.5 to 15.0 g/dl	13.35 ± 1.53	13.50 ± 1.18	12.98 ± 1.67	13.23 ± 1.35
TLC (4.0–10 thousand/mm3)	4000-10000/mm3	6897.73 ± 1410.51	7227.27 ± 1229.74	7322.22 ± 1632.33	7126.67 ± 1451.39
Platelet Count	1.5–4.5 lakh/mm3	2.79 ± 0.84	2.78 ± 0.77	2.71 ± 0.71	2.76 ± 0.67
Neutrophils	40–80%	57.05 ± 7.55	57.73 ± 7.40	55.52 ± 7.84	53.69 ± 6.64
Lymphocytes	20–40%	30.45 ± 5.85	32.28 ± 5.79	31.45 ± 6.43	31.07 ± 6.02
Eosinophils	1–6%	3.91 ± 2.54	4.22 ± 2.18	4.18 ± 3.53	4.21 ± 3.16
Monocytes	2–10%	6.82 ± 2.37	6.38 ± 1.99	7.22 ± 2.40	6.41 ± 2.09
SGOT	0–40 U/L	29.13 ± 14.58	30.63 ± 10.49	29.03 ± 12.22	28.30 ± 8.41
SGPT	0–41U/L	28.29 ± 13.69	28.99 ± 9.32	29.48 ± 21.50	28.27 ± 17.04
Serum urea	17–43 mg/dL	18.93 ± 4.38	20.18 ± 4.73	20.79 ± 6.19	21.88 ± 5.24
Serum creatinine	0.5–0.91 mg/dL	0.90 ± 0.17	0.87 ± 0.10	0.81 ± 0.18	0.86 ± 0.12
FBS	70–105 mg/dl	93.21 ± 16.88	99.51 ± 15.20	94.58 ± 11.98	96.37 ± 21.90

LVO- Lesser viscosity oil, **MVO-**Medium viscosity oil, **N-** number of participants, **ESR** – Erythrocyte sedimentation rate, **Hb** – Haemoglobin, **TLC** – Total leucocyte count, **SGOT** – Serum glutamic-oxaloacetic transaminase, **SGPT** - Serum glutamic-pyruvic transaminase, **FBS** – Fasting blood sugar.

Table 4
Preparation of oil of different Snehapaka and their indications.

S.No.	Type of Snehapaka	Methods of preparation	Proper signs of preparation	Signs for specific Snehapaka	Indications in Ayurveda
1.	Mridu sneha paka	In this process, oil or clarified butter is mixed with Specified amount of Kalka (paste of medicinal plants and minerals) and Dravadravyas (~medicated liquids like decoction, milk, butter milk, juice etc.) and these are subjected to moderate heating till the watery portion is completely evaporated.	There will be Stoppage of bubbling sounds and appearance of bubbles in oil. Appearance of clarity in oil. Paste used for preparation of oil does not adhere to the fingers. Paste attains perfect wick shape when rolled between thumb and index. paste is neither very hard nor very soft in texture	In this Paka, paste remain sticky, there is traces of water in oil and paste hence cracking sound is present during heating	Nasya [Ch. Sa.] Pana [Su. Sa]
2.	Madhyam sneha paka			In this Paka, paste remain non-sticky, Varti (wick shape structure) can be made of paste. Oil and paste is free from water hence there will be no cracking sound during heating. Froth appearance in oil and appearance of desired color, odor, and taste in oil	Basti, Pana [Ch. Sa.] Nasya, Abhyang [Su. Sa]
3.	Khara snehapaka			Paste become hard, rough, darkened, water-free, and dry. Color, odor, and taste may change	Abhyanga [Ch. Sa.] Basti, Nasya [Su. Sa]

Ch. SA. - Charak Samhita, Su. Sa. - Sushruta Samhita.

degradation in the nose, etc. The formulation type like dry powder or liquid also affects nasal delivery. In this trial, we used the formulation for *N. karma* which has greater lipophilicity due to its *Snehapaka*. Contact time between the drug and the nasal mucosa can be increased by higher viscosity of formulation and thereby increasing the time for permeation. Highly viscous formulations may also interfere with normal functions like mucociliary clearance and thus also alter the absorption of drugs. The higher viscous formulation may be retained for a longer time due to lower mucociliary clearance and this may increase the drug absorption. This may be the reason for better results of *N. karma* with MVO which was having higher viscosity in this study.

Specific measures are mentioned in Ayurveda to increase the lipophilicity of drugs. This specific measure is based on Ayurveda principles to prepare these lipid-based drugs for nasal administration. This is termed in Ayurveda classical texts as *Snehapaka*. *Sneha Kalpana/paka* may be defined as "A pharmaceutical process to prepare lipid-based drugs from the substances like *Kalka* (herbal paste of botanicals), *Kwatha* (decoction of Ayurveda botanicals), other medicinal liquid and lipids/oil as base material, taken in specific proportion and by subjecting them to unique heating pattern and duration to fulfill certain Ayurveda pharmaceutical parameters". These oleaginous medicaments are likely to be similar to liposomes in which nanoparticles comprise lipid bilayer membranes surrounding an aqueous interior [17]. Thus these formulations are able to impart the effects of lipid-soluble medicines and water-soluble medicines to the cells. According to the duration of heating, it may be *Mridu Snehapaka* (~oleaginous medicaments with lesser viscosity), *Madhyama Snehapaka* (~oleaginous medicaments with medium viscosity), and *Khara Snehapaka* (oleaginous medicaments with higher viscosity). The method of preparation, properties and their uses are summarized in the table [Table 4].

We also noticed the *Samyaka Lakshana* (proper signs) of *N. karma* during the procedures in each group of participants. No adverse event was noticed during the follow-up. No rescue medicine was needed for any participants during the trial and follow-up. No reported adverse event in this trial is an important finding as these adverse events were reported in the previously published trial in biomedicine. Various drugs like Zolmitriptan and Sumatriptan were tried in biomedicine through the nasal route. These drugs were reported to have side effects like the unusual taste, paraesthesia, dizziness, hyperesthesia in adults, nasal discomfort, rhinorrhoea, rhinitis, application site pain, dysgeusia, application site reaction, upper respiratory infection, nasopharyngitis, and sinusitis. Thus, these drugs had limited usage through nasal routes [18–22].

Various procedures as preparatory measures and post procedures measures –like medicated smoking and washing of buccal cavity with water mixed with *Tankan bhasma* are also part of *N. karma*. Thus, *N. karma* was a composite mechanism that included preparatory measures, nasal drug delivery, and post-procedures measures. These specific procedural measures ensure better nasal drug delivery without any adverse events.

Findings of this trial may be helpful in the selection of oil of different viscosities in the management of different intensity or chronicity of migraine.

5. Conclusion

Nasya with either LVO or MVO is having significant improvement in migraine. But the efficacy of *Nasya* with MVO was better. Hence *Nasya* with either LVO or MVO can be used according to episodic migraine or chronic migraine but *Nasya* with medium viscosity oil will give better results.

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Conflict of interest

Nil.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaim.2022.100662.

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