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Original article

Randomized Controlled Study to Evaluate Prophylactic Properties of Ayurvedic Treatment Protocol in Refractory and Chronic Migraine Patients

Vaidya Balendu Prakash [*1], Nitin Chandurkar [2], Vaidya Shikha Prakash [1], Shakshi Sharma [1], Sneha Tiwari [1]

[1]VCPC Research Foundation, Uttarakhand, India
[2]Ipca Laboratories Limited, Maharashtra, India

*Corresponding author: Vaidya Balendu Prakash, VCPC Research Foundation, Prakash Villa, Beside Rave Cinemas, Danpur, Rudrapur, Uttarakhand, India; *balenduprakash@gmail.com*

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Abstract

Background: Migraine is a disorder marked by recurrent episodes of headache. There is a subset of migraine patients who remain refractory to the conventional prophylactic and abortive therapies. This study aimed to assess the therapeutic role of an ayurvedic treatment protocol in patients who had chronic/ refractory migraine. ***Methods:*** This single-center, open label, randomized, controlled clinical trial compared the efficacy of ayurvedic treatment protocol to conventional treatment. Included patients were 18-65 years of age and met the diagnostic criteria for chronic/ refractory migraine. The patients were randomized in a 1:1 ratio to the ayurvedic treatment or conventional therapy at the baseline and were followed at regular intervals for 360 days. The primary outcome was reduction in the number of headache days in the last 3 months and the secondary outcomes were a reduction in the visual analog scale (VAS) score and migraine disability assessment score (MIDAS) as compared to the baseline. ***Results:*** Patients (n=154) were randomized to the two treatment groups with similar baseline demographic and clinical characteristics. The patients in ayurvedic treatment group had a greater reduction in the number of headache days, VAS score and MIDAS score at day 360 ($p<0.05$). Further, there were no reported medication-related adverse effects in either group. ***Conclusion:*** Ayurvedic treatment protocol is well tolerated and is associated with significant improvement in symptoms of chronic refractory migraine.

Keywords: ***Migraine, Refractory, Chronic, Ayurveda, Clinical trial***

Introduction

Refractory migraine is a headache that causes significant interference with functions or quality of life despite modification of triggers, lifestyle factors and adequate trails of acute and preventive medicines with established efficacy. The patients fail 3-4 adequate trials of preventive medicines, alone or in combination, from at least 2 of 4 drug classes including beta-blockers, anticonvulsants, tricyclics and calcium channel blockers. Patients should also fail adequate trials of abortive medicines, including both a triptan and dihydroergotamine (DHE) intranasal or injectable formulation and either non-steroidal anti-inflammatory drugs (NSAIDs) or combination analgesic, unless contraindicated. Refractory migraine patients must meet the International Classification of Headache Disorders, Second Edition (ICHD-2) criteria for chronic migraine or refractory migraine [1].

There is a constant upsurge in the prevalence of migraine globally. In United States, the incidences rose from 6.54% in 2003 to 9.69% in 2012 [2]. 5-8% migraineurs have chronic migraine and about 5% suffer from refractory migraine, with overall prevalence of RM/CM at around 2-3% [3]. The disease adversely affects an individual's personal, professional and social life causing moderate to severe debility and also substantial agony, frustration and financial burden [3]. In 2015, $5.4 million were spent on treatment of CM in the US [4].

The management of RM/CM is complicated and the conventional treatment causes moderate to severe side effects and badly affects the psychological state of its sufferers [5]. A North India based Ayurvedic clinical practice has reported sustainable and complete relief from migraine in significant number of cases by using an Ayurvedic Treatment Protocol, comprising of four herbo-mineral Ayurvedic preparations, Narikel Lavan, Numax, Rason Vati and Godanti Mishran [6,7].

These formulations are derived from Rasa Shastra in Ayurveda and have successfully passed through toxicological studies [8,9]. The present study was carried out under a competent neurologist to prove the stated prophylactic properties of Ayurvedic formulations in RM/CM patients.

Material and Methods

The study was carried at Department of Neurology, All India Institute of Medical Sciences, New Delhi between 1st April 2012 and 31st May 2016. Ethical clearance was obtained vide reference no. IEC/NP-276/2011 dated 03-10-2011. A tripartite agreement was made between investigators, participating institute and sponsoring body.

Study design and patient population

This is a randomized, open labelled, double arm comparative study conducted in a single tertiary care centre in India. The study protocol was approved by the institutional review board and the trial was registered with the clinical trial registry of India (Protocol No. Ipca/ATP/P III-10).

Adults aged 18–65 years who met the International Classification of Headache Disorders – 2nd Edition diagnostic criteria for migraine or chronic migraine and who remained refractory to treatment with conventional prophylactic medications were included in the study. Refractory migraine was defined as headaches causing significant interference with function or quality of life despite modification of triggers and lifestyle factors and refractory to treatment with three or more adequate trials of preventive medications from at least 2 of the 4 drug classes, including β blockers, tricyclic antidepressants, calcium channel blockers and anticonvulsants [1]. Informed consent was obtained from all patients.

Patients with secondary headaches, concurrent chronic diseases, and those with a history of substance abuse were excluded from the study. Additionally, patients who were on any medications for conditions other than migraine and/or those with a history of hypersensitivity to any medication were also excluded from the study.

Visits and Randomization

At the initial screening visit, a detailed clinical history was obtained and physical examination was performed and the patients were assessed for the inclusion and exclusion criteria. In addition, baseline investigations including a complete hemogram, blood urea nitrogen, serum creatinine, bilirubin, liver transaminases, fasting blood glucose, and cranial non-contrast computed tomography scans were performed for all patients.

Eligible patients were randomized in a 1:1 ratio to receive either ayurvedic treatment protocol or conventional treatment through selection of sealed opaque envelopes. The ayurvedic treatment protocol used in this study is shown in **Table 1**. All patients were assessed for headache days, pain intensity, headache frequency, duration and associated symptoms in the seven subsequent visits on days 30, 60, 90, 120, 150, 180 and 360.

Table 1: Ayurvedic treatment protocol

Name of formulation	Dose	Vehicle	Schedule
Narikela Lavana (powder)	1 gram, 12 hourly	200 grams yoghurt + 50 mL water	Before breakfast and dinner
Numax	500 mg, 12 hourly	Water	During breakfast and dinner
Rasonadi Vati	500 mg, two tablets 8 hourly	Hot water	After breakfast, lunch and dinner
Godanti Mishran	500 mg, 24 hourly	Mishri	At bedtime

Outcomes

The primary outcome was mean change in the number of headache days in the last three months from the baseline and the secondary outcome measures were change in the visual analog scale (VAS) score and migraine disability assessment score (MIDAS) as compared to the baseline. In addition, we also assessed the proportion of patients reporting relief from the associated symptoms of migraine.

Safety measures

Self-reported medication related adverse effects were recorded at each follow-up visit. Detailed physical examinations were performed at each visit to screen for any apparent side effects. Further, all baseline blood investigations were repeated at the final visit to look for any changes from the baseline.

Sample size calculation and statistical analysis

The sample size was calculated considering a 10% difference in reduction of migraine frequency between the two groups. Setting the type 1 error at 0.05 and considering a 20% dropout rate, sample size in each arm was calculated as 77 patients, providing 80% statistical power to the study.

Intention to treat analysis was performed and the last observation was carried forward to impute for the missing values for patients who were lost to follow up after at least one recorded post-randomization efficacy measurements. The baseline characteristics of the two groups were compared using chi square for categorical variables and independent t-test for continuous variables. The change in primary and secondary outcome measures from the baseline was calculated for each group independently and was compared between the two groups. Further, proportion of patients reporting relief from migraine associated symptoms were compared between the two study groups.

Monitoring

The project was well monitored and four periodical progress reports were submitted by the investigators to the sponsoring body (data on file).

Results

During the study period, 257 patients were screened for the eligibility criteria. Ultimately, 154 patients were randomized in a 1:1 ratio to receive either ayurvedic treatment protocol or the conventional treatment. Of these, 7 patients from the ayurvedic treatment group discontinued after the baseline visit and 1 patient from the conventional treatment group discontinued after the first follow-up visit on day 30. With the intention to treat analysis, last observations were used to impute the missing values for the one patient in the conventional treatment group whereas the 7 patients with no efficacy measurements were excluded from the further analysis.

The mean ± SD age of the study population was 34.6 ± 9.6 years and 72.1% were females. The mean ± SD duration of migraine was 4.9 ± 4.6 years and the mean ± SD VAS and MIDAS scores at baseline were 8.2 ± 0.77 and 41.5 ± 9.2, respectively. The two treatment groups were similar in the demographic and clinical characteristics at baseline except for significantly higher MIDAS score in the ayurvedic treatment group (**Table 2**).

Table 2: Baseline demographics and clinical characteristics

	Conventional Treatment (n=77)	Ayurvedic treatment (n=77)	p-value
Age (years)	34.74 (9.33)	34.53 (10.00)	0.894
Female	59 (76.62)	52 (67.53)	0.209
History of migraine (years)	4.51 (3.83)	5.33 (5.22)	0.266
Migraine days in 3 months	56.48 (16.45)	55.19 (18.48)	0.649
Nausea	63 (81.82)	63 (81.82)	1.000
Vomiting	53 (68.83)	51 (66.23)	0.731
Photophobia	69 (89.61)	68 (88.31)	0.797
Phonophobia	60 (77.92)	59 (76.62)	0.848
VAS score	8.21 (0.80)	8.19 (0.74)	0.917
MIDAS score	38.79 (8.58)	44.22 (9.02)	**<0.001**
All categorical variables are represented as n (%), all continuous variables are represented as mean (SD) VAS- Visual Analog Scale, MIDAS- Migraine Disability Assessment			

Outcome measures

The difference in the primary and secondary outcomes from the baseline and between the two treatment groups is shown in **Table 3**. The primary outcome measure, that is, the reduction in the number of headache days from baseline was 44.0 days for the ayurvedic treatment group and 36.5 days for the conventional treatment group with an average of 7.5 days greater reduction (95% CI = 2.1 – 13.0) in the ayurvedic treatment group (p<0.01).

The secondary outcome measures, that is, the reduction in the VAS score at day 360 was 6.0 for the ayurvedic treatment group and 5.4 for the conventional treatment group. Similarly, the reduction in the MIDAS score at day 360 was 36.7 for the ayurvedic treatment group and 27.7 for the conventional treatment group. The ayurvedic treatment group had a significantly greater reduction in both the scores when compared to the conventional treatment group (p<0.01) (**Figure 1 and 2**).

Table 3: Change in primary and secondary end-points from the baseline

	Conventional Treatment* (n=77)	Ayurvedic treatment* (n=70)	Difference in Means** (95% CI)	β Coefficient (95% CI)	p-value***
Primary endpoint					
Migraine days in 3 months	-36.45 (1.68)	-43.99 (2.24)	-7.53 (-13.00 – -2.07)	-0.01 (-0.01 – 0.00)	**0.007**
Secondary endpoints					
VAS					
Day 90	-2.32 (0.08)	-2.49 (0.11)	-0.16 (-0.10 – 0.42)	-0.06 (-0.17 – 0.04)	0.219
Day 180	-4.49 (0.12)	-4.84 (0.11)	-0.35 (-0.67 – -0.03)	-0.09 (-0.17 – -0.01)	**0.035**
Day 360	-5.35 (0.15)	-5.99 (0.13)	-0.64 (-1.02 – -0.25)	-0.11 (-0.17 – -0.04)	**0.002**
MIDAS					
Day 90	-10.68 (0.81)	-17.71 (0.69)	-7.04 (-9.17 – -4.91)	-0.03 (-0.04 – -0.02)	**<0.001**
Day 180	-19.99 (1.22)	-29.43 (0.96)	-9.44 (-12.54 – -6.34)	-0.02 (-0.03 – -0.01)	**<0.001**
Day 360	-27.66 (1.32)	-36.66 (0.94)	-9.00 (-12.25 – -5.75)	-0.02 (-0.03 – -0.01)	**<0.001**
** Difference in means (SE) from baseline. ** Difference in mean reduction between ayurvedic and conventional treatment groups. *** p values are for ayurvedic treatment group vs conventional treatment group. VAS- Visual Analog Scale, MIDAS- Migraine Disability Assessment*					

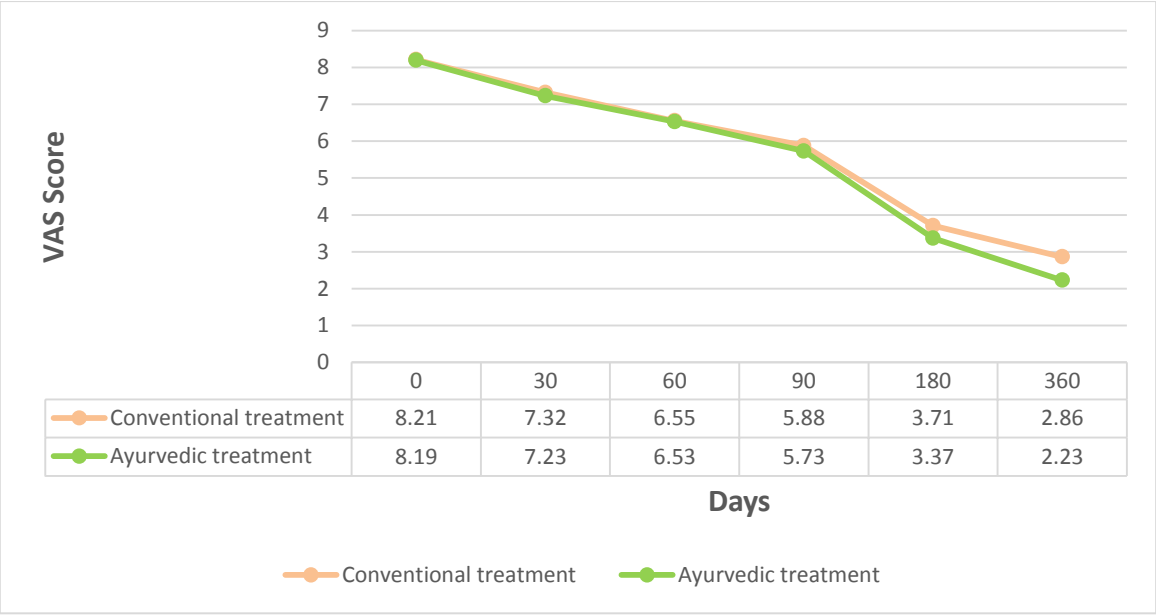

Figure 1: Effect of conventional and ayurvedic treatment on Visual Analog Score (VAS)

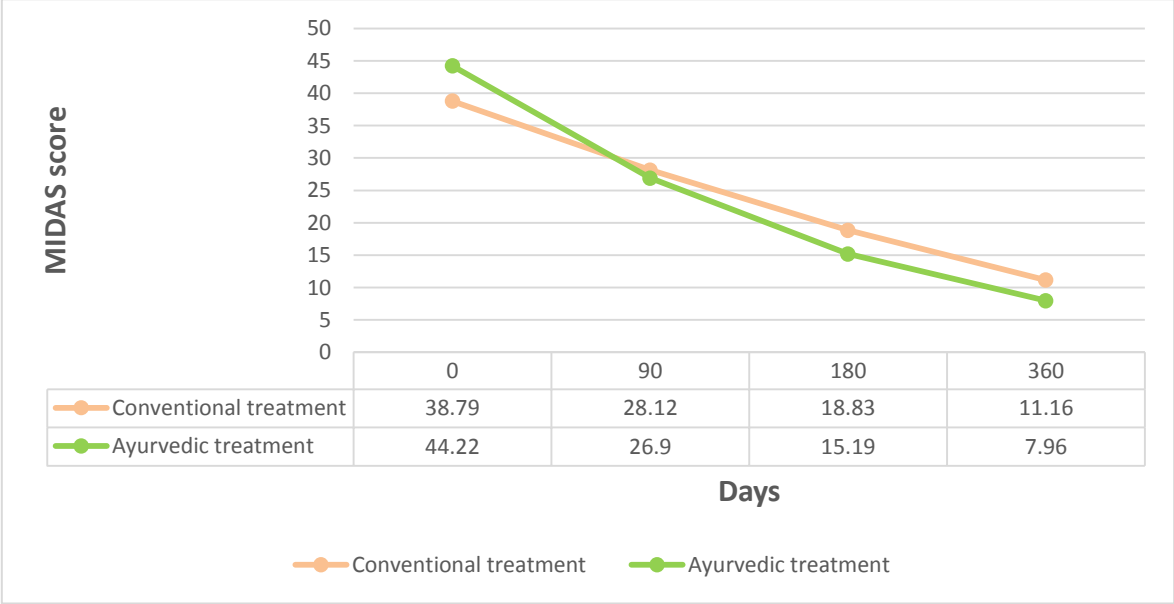

Figure 2: Effect of conventional and ayurvedic treatment on Migraine Induced Disability Assessment Scale (MIDAS)

Associated symptoms

A greater proportion of patients reported relief from all associated symptoms of migraine in ayurvedic treatment group as compared to the conventional treatment group. However, the difference was statistically significant for nausea, photophobia, phonophobia and fatigue ($p<0.05$) (**Table 4**).

Safety assessment

No serious adverse effects were reported at any of the follow-up visits in either treatment group. Additionally, the physical exams and blood investigations of all patients remained unchanged from the baseline.

Table 4: Percentage of subjects in ayurvedic and conventional treatment groups reporting relief from symptoms associated with migraine

	Conventional treatment (%)	Ayurvedic treatment (%)	p value
Nausea	37.31	63.93	**0.003**
Vomiting	85.19	95.65	0.101
Photophobia	40.58	59.38	**0.031**
Phonophobia	63.33	84.62	**0.013**
Fatigue	44.44	68.63	**0.014**
Blurring of vision	77.78	89.29	0.258
Otalgia	86.36	86.96	0.953
Tinnitus	83.33	100.00	-
Perspiration	56.52	63.64	0.491
Heartburn	88.00	95.83	0.338
Belching	82.22	88.57	0.433
Flatus	91.30	100.00	-
Constipation	79.59	80.00	0.962

Discussion

This study demonstrates the safety and efficacy of ayurvedic treatment protocol in patients with chronic refractory migraine. As compared to the conventional treatment, ayurvedic treatment was associated with greater reduction in the number of headache days, VAS scores, MIDAS scores as well as the associated symptoms of migraine. Further, ayurvedic treatment protocol had no serious adverse effects noted in the first 360 days of it use.

Chronic refractory migraine is a difficult-to-treat complex disorder. As a result, patients suffering from it often seek novel approaches to treatment. A variety of herbal medications like Tenacetum Parthenium, Petasites Hybridus, have been studied for the treatment of headaches [10,11]. In addition, alternate medicinal systems such as, yoga, relaxation, and meditation have also shown efficacy in the treatment of headaches. In general, chronic pain is among the most common indications for the use of complementary and alternative therapies and their use in chronic migraine is particularly increased due to the fear of adverse effects and lack of efficacy of the conventional medications [12]. The results shown in our study are highly encouraging for the use of ayurvedic treatment protocol in patients who are refractory to the conventional prophylactic medications. The four Ayurvedic formulations used in this study are classical Ayurvedic formulations which have shown cumulative prophylactic properties in RM/CM patients. These formulations have also undergone pharmacological studies. The data of the study shows that these formulations have no analgesic, anti-inflammatory, anti-histamine, anti-5HTeffects or effects on general CNS activity, or behavioural and hemodynamic parameters, alone or in combination (data on file).

This randomized controlled clinical trial was carried on an adequate sample size and could be termed as preliminary ‘proof of efficacy’ study to verify the reported therapeutics of Ayurvedic treatment protocol. Further pharmacological and multicentre open label/ double blind clinical trials should be carried to understand phenomenal nature of Ayurvedic treatment.

In conclusion, ayurvedic treatment protocol is well tolerated and is associated with significant improvement of symptoms in patients with chronic refractory migraine. There is a need for more carefully conducted large prospective studies to clearly define the therapeutic role and assess the safety of ayurvedic treatment in patients with migraine.

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Conflict of interest

Authors declare no conflict of interest.

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