

Efficacy and safety of panchgavya GHRIT along with flunarizine in prophylaxis for migraine patients: a comparative study

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ABSTRACT

Background: Propranolol and flunarizine have proven to be useful tools in migraine prophylaxis. This trial aims the comparison of the efficacy of flunarizine, flunarizine and placebo and flunarizine and panchgavya ghrith in migraine prophylaxis.

Methods: The present study was a prospective, randomized, open-label, blinded-endpoint trial. Patients with chronic migraine were randomized (1:1:1) to flunarizine and flunarizine and placebo and flunarizine and panchgavya ghrith in three treatment groups. The study was carried out in outdoor patients in the department of Psychiatry, T.S. Mishra Medical College and Hospital, Lucknow and K.G.M.U, Ayush Department, Lucknow after clearance from Institutional Ethical Committee. Data was analysed using SPSS software.

Results: The prevalence of migraine was found to be higher in the age group greater than 30 years and females. Overall there was more reduction in CGI scores in flunarizine with panchgavya ghrith and the other two groups equally at the end of 4, 6 8 and 10 weeks. Decrease in MIDAS score was observed after the therapy. Clinical Global Impression rating scale employed revealed that to start with subjects scored 7 which stands for pathology interfering in many life functions which reduced drastically in Group C as compared to Group B and Group A in descending order. Pain scales namely VAS (visual analogue scale), NPRS (Numeric Pain Rating Scale), VRS (verbal rating scale) when employed denoted there was decreased migraine frequency, decreased perception of pain, less intake of abortive medication consumed by subjects implying there were reduction in number of migraine days and there was decrease in the abortive medications taken for the same. Group C scored better on pain scales followed by Group B and Group A. Lower proportion of individuals in group C had Behavioural Toxicity and Neurological Side effects as compared to Group A and B.

Conclusions: Panch gavya ghrith when administered along with flunarizine was more efficacious and safe when compared with other two groups. However large multicentric RCTs of long duration and involving more number of subjects are required to ascertain these facts.

Keywords: Flunarizine, Migraine, Panch gavya ghrith

INTRODUCTION

Migraine is a widespread, chronic and intermittently disabling disorder characterized by recurrent headaches with or without aura.¹ The prevalence of migraine is about 6-8% in men and 12-15% in women as per the conducted studies. Approximately 3000 migraine attacks occur every day for each million of the general population which impress upon the incidence and prevalence of migraine.² The rate of migraine varies

globally, and more so with the data available in many countries at present, recent anecdotal evidence suggests higher rates in certain places like India.³ Recurrent migraines can be disabling: the cost of missed workdays and impaired performance associated with migraines in the United States totals around \$13 billion each year.^{4,5} Preventive therapy, which can reduce the frequency of migraines by 50 percent or more, is used by less than one half of persons with migraine headache.⁶ In Ayurveda *Arddhavabhedaka* - a comparable clinical condition of

migraine is a commonly occurring vascular headache presenting with pain on one half of the head as cardinal feature. It is described as a separate clinical entity in the classics of Charaka and Susruta while Vagbhata included this condition in the classification of *vataja-siroroga*. Pain in one half of the head may also appear as a symptom in various conditions viz. *anyatovata (netraroga)*, *vata-paryayam (netraroga)* and *ardditavata (vataroga)*. According to Ayurveda, action of a drug is based on its guna, veerya, vipaaka and prabhaava. These as themselves or as combinations determine the status of drug action in the body. Fate of the drug always depends on rasapancaka and it goes in line with modern pharmacodynamics.⁷ Besides that the drug action also depends the action of agni on that particular drug. Most of the Ayurvedic drugs act only after absorption and are said to have systemic or general action. Many a time, the term 'action' and 'effect' of a drug are used as synonyms. Many a drug has been mentioned in Ayurvedic psychiatry. Panchagavya gritha (PGG) is mentioned in Apasmara chikitsa. It is one of the commonly used yogas not only for apasmara, but also many other psychiatric conditions including OCD, Migraine Depression and types of Schizophrenia in the form of oral route of drug intake and nasya karma. The combination contains 5 ingredients.

Gos'akr't (Cow dung), Godadhi (Curd), Goksheera (Milk), Gomootra (Cow's urine) and Goghr'ta (Ghee).⁸ All the drugs are taken in equal quantities and the gritha is prepared as per the common preparatory techniques regarding gritha.⁹ Literature revealed that cow ghee, cow milk and cow urine possesses intellect and memory enhancing, rejuvenating and aphrodisiac activities.¹⁰⁻¹² Cow dung juice has antibacterial and cow curd has aphrodisiac activity.^{13,14} Similarly various researches are reported on single cow products for their effects on CNS. Thus combination of these products may show cumulative desired effect of PGG on cognition i.e. improvement of learning and memory.

Previously PGG has been assessed for anticonvulsant, hepatoprotective and antiepileptic activities; however no work has been carried out on assessment of anti migraine activity of PGG. Sometimes, if migrainous headaches are recurring twice a month or more, a prophylactic treatment is required.¹⁵⁻¹⁷ There is a variety of medication usually employed in the migraine prophylaxis, a hint that none is entirely effective. Moreover, usually there are patients who do not respond to one or more prophylactic drugs. Besides, there are individual differences in the responsiveness to different prophylactic agents and even sometimes, an inability to sustain an initial good response to a particular agent. Such facts may be arguments for the concomitant use of two modalities of drugs in migraine prophylaxis. Propranolol and flunarizine have proven to be useful tools in migraine prophylaxis.¹⁸⁻²¹ This trial aims the comparison of the efficacy of flunarizine, flunarizine and placebo and flunarizine and panchgavya ghrit in migraine prophylaxis.

METHODS

The present study was a prospective, randomized, open-label, blinded-endpoint (PROBE) trial. Patients with chronic migraine (CM) were randomized (1:1:1) to flunarizine and flunarizine and placebo and flunarizine and panchgavya ghrit (PGG) in three treatment groups. The study was carried out in outdoor patients in the department of Psychiatry, T.S. Mishra Medical College and Hospital, Lucknow and K.G.M.U, Ayush Department, Lucknow after clearance from Institutional Ethical Committee. Psychiatrist had enrolled participants, administered scales and assessed the clinical outcomes. Side effect monitoring was done and by a pharmacologist and a psychiatrist using DOTES scale. Nasya karma of panchgavya ghrit was done and taught to subjects attendant by competent Ayurvedic practitioner in O.P.D setting. The trial was conducted from September 2016 to January 2017. The patients were included in the study after fulfilling the inclusion/ exclusion criteria after obtaining full informed consent as diagnosed in psychiatry OPD of T.S. Mishra Medical College and Hospital. Systematic Random Sampling was applied and concealment was done by envelop method. Statistician had generated allocation sequence and assigned participants to their respective groups. The sample size was 60.

Inclusion criteria

Inclusion Criteria was ICHD-IIR criteria for CM (as reported by the patient). Experienced ≥ 7 days of headache lasting ≥ 30 min during T0 (-2 week to 0 week), On ≥ 4 of these days, subjects were required to have experienced migrainous headache, patients could receive preventive medications (medications for acute attack) other than the medications given during study period, with and without medication overuse, Subject > 10 years of age, either gender, headache history > 2 years, willing to follow the dietary restriction, willing to complete daily diary, willing to take the medication Or comply with procedure during the entire study period.

Exclusion criteria

Tension-type headache, cluster headache, and other primary headaches, secondary headache and other neurological disease, relatively severe systemic diseases (cardiovascular disease, acute infectious disease, hematopathy, endocrinopathy, allergy, and methysis), headache caused by otorhinolaryngology diseases or intracranial pathological changes, oral contraceptives, pregnancy, or lactation period, use of prophylactic migraine medication in the last 3 months, participation in another clinical trial, headache type other than CM, migraine onset after the age of 60 years, previous history of migraine prophylaxis before enrollment, history of hepatic or renal disorder, nephrolithiasis or other severe systemic disease, severe depression. Marked depression, anxiety or psychosis, major medical illness under

treatment, clotting disorders, more than 2 visits/month for mental healthcare. Use of any other alternative medication during study apart from rescue medication ultracet a combination of tramadol 37.5mg and acetaminophen 325mg as and when required.

Primary outcome measures were to assess reduction of total number of migraine days, quality of life and comparison of side effects in three groups Secondary outcome measures were to assess the disability associated with migraine, reduction of number of days of acute abortive medication intake and, reduction of number of acute abortive medication tablets taken.

RESULTS

Majority of patients were aged between 31-45 years and were females in all the three groups. A higher proportion of patients had duration of migraine less than 10 years and had a positive family history of migraine (Table 1). The prevalence of migraine was found to be higher in the age group greater than 30 years approximately twice as compared to less than 30 years age group, females were effected about thrice as compared to males, duration of illness was upto 10 years in maximum subjects, family history was positive in majority of subjects (Table 1). Around 80% of the patients were non-vegetarian and details of the prior treatment indicated that 41(68%) patients were totally dependent on allopathic medicine; 30 (50%) patients had tried both allopathic and alternative medicine such as Homeopathy, Unani/ Siddha, Ayurveda. It was found that exertion, lack of sleep and hunger were the three most important factors for aggravating migraine, at the time of enrollment all the patients reported more than six attacks in a year. Majority of patients of those who were enrolled had migraine attack once a week. Most complained of nausea, photo phobia, phono phobia, and vomiting as associated symptoms. A total of 60 patients were screened and relief in headache started to develop after 4 weeks and became conspicuous after 6weeks however patient fared much better, with better compliance less drop outs and minimal side effects in Group C.

Overall there was more reduction in CGI scores in flunarizine with panchgavya ghrit and the other two groups equally at the end of 4, 6 8 and 10 weeks. However it was not statistically significant (p>0.05) (Table 2).

Decrease in MIDAS score was observed after the therapy. At the start of therapy most number of patients had Grade IV (severe disability)which came down to Grade II in group A and B and Grade I in group C inferring that little or no disability was observed in third group however mild disability was still present in Group I and II.

Table 1: Distribution of patients according to Sociodemographic variables.

Variables	Flunarizine group (n=20)		Flunarizine and placebo group (N=20)		Flunarizine and panchgavya ghrit (N=20)	
	N	%	N	%	N	%
Age (in yrs)						
Upto 30	6	30	7	35	6	30
31-45	14	70	13	65	14	70
Gender						
Male	5	25	4	20	6	30
Female	15	75	16	80	14	70
Duration of migraine						
0-10 years	10	50.0	11	55.0	12	60.0
11-20 years	5	25.0	5	25.0	4	20.0
21-30 years	5	25.0	4	20.0	4	20.0
Family history of migraine						
Present	14	70.0	15	75.0	14	70.0
Absent	6	30.0	5	25.0	6	30.0

Table 2: Change in CGI Score from Baseline among the patients.

Change from baseline with time		Flunarizine (n=20)			Flunarizine with placebo (n=20)			Flunarizine with panchgavya ghrita (n=20)			chi sq, p-value
		Same	Decrease	Increase	Same	Decrease	Increase	Same	Decrease	Increase	
After 2 weeks	No.	12	7	1	8	10	2	9	11	-	3.83, 0.430
	%	60	35	5	40	50	10	45	55	0	
After 4 weeks	No.	10	9	1	7	12	1	7	13	-	2.51, 0.642
	%	50	45	5	35	60	5	35	65	0	
After 6 weeks	No.	8	12	--	7	13	--	6	14	--	0.440, 0.803
	%	40	60	0	35	65	0	30	70	0	
After 8 weeks	No.	7	13	--	7	13	--	5	15	--	0.616, 0.735
	%	35	65	0	35	65	0	25	75	0	
After 10 weeks	No.	6	14	--	6	14	--	3	17	--	1.37, 0.504
	%	30	70	0	30	70	0	15	85	0	

Table 3: Mean change in parameters pertaining to migraine scores from baseline in three groups.

Parameter	Group	Day								
		0	7	14	28	42	56	70	84	
CGI	Group 1	7								
	Group 2	7								
	Group 3	7								
CGI-I	Group 1		4	3	3	3	2	2	1	
	Group 2		4	3	3	2	2	1	1	
	Group 3		3	3	2	2	1	1	1	
MIDAS	Group 1	26								8
	Group 2	27								6
	Group 3	29								5
VAS	Group 1	10	9	8	6	5	3	2	1	
	Group 2	10	9	7	6	5	4	2	1	
	Group 3	10	7	5	3	3	1	1	1	
VRS	Group 1	Severe	Severe	Severe	Moderate	Moderate	Mild	Mild	Mild	
	Group 2	Severe	Severe	Severe	Moderate	Moderate	Moderate	Mild	Mild	
	Group 3	Severe	Severe	Moderate	Mild	Mild	Mild	Mild	Mild	
NPRS	Group 1	8.33	7.33	7	6	5	3.33	2.33	1.33	
	Group 2	8.66	8.33	7.66	6	5.33	4.33	2.33	1.33	
	Group 3	9	7	5	3.33	2	1	1	0.66	

Table 4: Side effects assessed by DOTES.

Side effects assessed by DOTES	Group A (Flunarizine)								Group B (Flunarizine with placebo)								Group C (Flunarizine with panchgavya ghrit)							
	0	14	28	42	56	70	84	0	14	28	42	56	70	84	0	14	28	42	56	70	84			
a. Behavioural toxicity																								
Insomnia	-	1	2	4	3	2	2	-	1	2	2	2	1	1	1	2	1	1	-	-	-			
Drowsiness	-	2	4	5	4	3	3	-	3	5	4	4	4	3	1	4	3	2	1	-	-			
b. Neurological																								
1. Rigidity	-	2	3	2	1	1	1	-	3	3	2	1	1	-	-	2	1	-	-	-	-			
2. Tremors	-	3	3	2	2	1	1	-	3	3	2	1	-	-	-	1	1	-	-	-	-			
c. A.N.S and G.I.T																								
1. Dry mouth	-	4	3	2	1	-	-	-	3	2	1	1	-	-	-	2	1	-	-	-	-			
2. Blurred vision	-	-	1	2	-	-	-	-	-	2	1	-	-	-	-	-	-	-	-	-	-			
3. Constipation	-	3	2	2	1	-	-	-	-	2	1	1	-	-	-	-	-	-	-	-	-			
4. Nausea	-	2	4	6	4	2	2	-	2	3	4	3	3	2	-	4	3	3	2	1	-			
5. Diarrhoea	-	1	2	2	-	-	-	-	1	2	2	-	-	-	-	3	2	2	1	-	-			
d. Others																								
1. Dermatologic (RASH)																								
1. Dermatologic (RASH)	-	2	2	1	-	-	-	-	2	1	1	-	-	-	-	1	-	-	-	-	-			
2. Weight gain																								
2. Weight gain	-	-	3	3	2	2	1	-	3	3	2	2	2	2	-	2	2	1	-	-	-			

Clinical Global Impression rating scale employed revealed that to start with subjects scored 7 which stands for pathology interfering in many life functions which reduced drastically in Group C as compared to Group B and Group A in descending order. The implications were

that there were rapid rate of recovery in clinical status of Group C as compared to other two groups. Pain scales namely VAS (visual analogue scale), NPRS (Numeric Pain Rating Scale), VRS (verbal rating scale) when employed denoted there was decreased migraine

frequency, decreased perception of pain, less intake of abortive medication consumed by subjects implying there were reduction in number of migraine days and there was

decrease in the abortive medications taken for the same. Group C scored better on pain scales followed by Group B and Group A (Table 3).

Table 5: Side effect and symptoms associated with migraine reported by the patient, observed by the clinician or elicited by the therapist.

Side effects reported	Group A								Group B								Group C							
	0	14	28	42	56	70	84	0	14	28	42	56	70	84	0	14	28	42	56	70	84			
Anxiety	-	2	2	1	-	-	-	-	2	1	1	-	-	-	-	-	-	-	-	-	-	-		
Depression	-	2	1	-	-	-	-	-	2	1	-	-	-	-	-	-	-	-	-	-	-	-		
Dizziness	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Sedation	-	2	1	1	-	-	-	-	2	2	1	-	-	-	-	1	-	-	-	-	-	-		
Fatigue	-	2	1	-	-	-	-	-	2	1	-	-	-	-	-	-	-	-	-	-	-	-		
Vertigo	-	3	2	1	-	-	-	-	2	2	1	-	-	-	-	-	-	-	-	-	-	-		
Headache	-	2	1	-	-	-	-	-	2	1	-	-	-	-	-	-	-	-	-	-	-	-		
Increased appetite	-	3	2	-	-	-	-	-	3	2	-	-	-	-	-	-	-	-	-	-	-	-		
Epigastric pain	-	2	1	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-		
Heart burn	-	3	3	2	-	-	-	-	3	3	2	1	-	-	-	-	-	-	-	-	-	-		
Vomiting	-	2	1	-	-	-	-	-	2	1	-	-	-	-	-	-	-	-	-	-	-	-		
Muscle ache	-	2	1	-	-	-	-	-	2	1	-	-	-	-	-	-	-	-	-	-	-	-		
Menstrual irregularity	-	3	3	2	2	-	-	-	2	2	1	-	-	-	-	-	-	-	-	-	-	-		
Photophobia	-	5	4	3	2	1	-	-	4	3	3	2	1	-	-	3	2	1	-	-	-	-		
Phonophobia	-	4	3	1	-	-	-	-	4	3	2	1	-	-	-	3	2	1	-	-	-	-		

Lower proportion of individuals in group C had Behavioural Toxicity and Neurological Side effects as compared to Group A and B (Table 4). Lower number of patients reported side effects associated with migraine in group C as compared to group A and B (Table 5).

DISCUSSION

Since the pharmaceutical treatment of migraine is complex, with no agreed upon guidelines individuals often need abortive medication during acute attacks and some prophylactic measure to reduce attacks. Some abortive drugs such as Triptans and ergotamine tartrate are often expensive and not commonly used in resource-poor countries, resulting in a significant amount of pain and disability.²² Another problem is the actual overuse of such medications which causes ‘medication overuse headache’ (MOH), further complicating management strategies.²³

A large percentage of patients do not respond to pharmacological interventions for migraine headache, develop unacceptable side-effects, or are reluctant to take medications.²⁴ As a result many patients resort to many complementary and alternative therapies like acupuncture, biofeedback therapy, relaxation therapy, herbal remedies and vitamin or mineral supplementation.²⁴⁻²⁶ Recent studies have demonstrated the effectiveness of acupuncture and Yoga in the

reduction of migraine headache. The use of complementary and alternative medicine (CAM) in migraine is a growing phenomenon which, though increasingly widespread, is poorly understood.²⁷⁻²⁹ Ayurveda is a traditional medical system used by a majority of India's 1.1 billion population.³⁰ Though Ayurvedic therapy is popular among migraine sufferers, there are very few studies which have compared pharmacotherapy pertaining to combination of two lines of treatment aiming for the holistic view of treatment with aim of increasing compliance ,increasing potency of drugs and reducing side effects caused by allopathic medicines when administered alone. Migraine was distinguished from common headache by Tissot in 1783 for the first time who ascribed it to a supra-orbital neuralgia provoked by reflexes from the stomach, gall bladder or uterus. Later, migraine was classified as a neurological disorder. Our hypothesis is quite similar to Tissot's idea on the pathogenesis of migraine, viz. that it usually arose from stomach disturbance.³¹ Incidentally, there is a close correlation between the symptoms of migraine with those of *Amla-pitta* (state of acid-alkali imbalance in the body) causing symptoms such as: *brahma*(confusion), *moorcha* (fainting), *aruchi* (anorexia), *aalasya* (fatigue), *chardi* (vomiting), *prasek* (nausea), *mukhmadhurya* (sweetness in the mouth) and *shiroruja* (headache). The correlation between the cause and symptoms of *Amla-pitta* match the current diagnosis criteria of migraine.

Complimentary and Alternative Medicine (CAM) is often perceived by the public to be more helpful than conventional care for the treatment of headache.³² This study is also in line with the prior ayurvedic researchers which stress upon effectiveness safety and tolerability of ayurvedic medications in migraine prophylaxis.³³ This study is first of its kind as we could not find any previous study from literature search reporting a comparison between the efficacy of flunarizine, flunarizine and placebo and flunarizine and panchgavya ghrith in migraine prophylaxis. The non-cross-over design had subjects having migraine without aura, although less powerful than the cross-over design, had the advantage of avoiding the carryover effect, a feature of great importance in migraine prophylaxis trials. From this comparative study we can make a preliminary assessment that combination of standard prophylaxis in allopathic medication along with panch gavya ghrith caused decrease in measures of symptom severity, better tolerability, lesser side effects, better compliance, lesser drop outs, good treatment response and efficacy among patients with migraine, implying that panch gavya ghrith when administered along with flunarizine was more efficacious and safe when compared with other two groups. However large multicentric RCTs of long duration and involving more number of subjects are required to ascertain these facts.

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