Original Article

Effectiveness of Magnesium Phosphoricum 6x in Comparison with Individualized Homeopathic Treatment of Primary Dysmenorrhoea: An Open-label, Randomized, Pragmatic, Equivalence Trial

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ABSTRACT

Background: Primary dysmenorrhea refers topainful menstruation in the absence of any pelvic pathology.Itis a common and often debilitating gynaecological complaint among adolescent and adult females, affecting their quality of life. According to homeopathic philosophy, medicines are prescribed based on individualization as per the totality of symptoms. However, different literature also shows the clinical utility of *Magnesiumphosphoricum* (MP) in lowering pain of primary (spasmodic) dysmenorrhea, especially in 6X potency. We aimed to evaluate the effectiveness of MP 6X against individualized homeopathic medicines (IHMs).

Methods: An open-label, randomized, two parallel arms, pragmatic trial was conducted at the obstetrics and gynecology outpatient department of The Calcutta Homeopathic Medical College and Hospital, West Bengal. Sixty females sufferingfrom primary dysmenorrhea were randomized to receive either MP 6X (n=30) or IHMs (n=30). The primary outcomemeasure was pain intensity measuring0-10 numerical rating scale (NRS), assessed on days 1 and 2 of menstruation, measured at baseline and every month up to 3 months. The secondary outcome was a verbal multidimensional scoring system (VMSS), measured at the baseline and after 3 months. Baseline adjusted comparative analysis was carried out using SPSS® on intention-to-treat sample to detect group differences.

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Results: Seven participants dropped out (MP:3, IHMs:4).In the IHMs group, *Natrum muriaticum* was the most frequently prescribed medication. Statistically significant intra-group changes over different timepoints were elicited in both groups (all $P< 0.05$, paired *t*-tests, andrepeatedly measured one-way analysis of variance).Except on the 2nd day of the menstrual cycle after 1 month (P_{0-1}=0.350, unpaired *t*-test), group differences in menstrual pain NRS on day 1 [P_{0-1}=0.007, P_{0-2}=0.0004, P_{0-3}=0.0001] and day 2 [P_{0-2}=0.004, P_{0-3}=0.020] and VMSS [total P_{0-3}=0.0001, physical P_{0-3}=0.0001, psychological P_{0-3}=0.0001, and social P_{0-3}=0.001] were statistically significantly favoring IHMs against MP 6X. Still, after 3 months of intervention, non-inferiority was demonstrated by MP 6X against IHMs in pain NRS on the 1stday of menstrual flow [mean difference=2.0, lower 95% confidence limit 1.1, P<0.001], on the 2ndday [mean difference=1.3, lower 95% confidence limit 0.5, P<0.001] and in VMSS total scores [mean difference=11.6, lower 95% confidence limit 8.3, P<0.001].

Conclusion:MP 6X was found to be non-inferior to IHMsin the treatment of primary dysmenorrhea. Further exploration is warranted.

Keywords: Dysmenorrhea, Homeopathy, *Magnesium phosphoricum*, Non-inferiority trial

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Introduction

Menstruation is a natural phenomenon that occurs throughout the reproductive years of women.Most females experience a certain degree of pain and distress during their menstruation period.[1]Dysmenorrhea refers to the pain or discomfort associated with a menstruation of sufficient magnitude that can refrain a woman from usual functioning for a day or two each month. It is of two types: primary and secondary. Primary dysmenorrhea refers to menstrual pain,which is not due to any evident pathology.On the other hand, secondary dysmenorrhea is defined as menstrual pain due to pelvic pathology.Prevalence of dysmenorrhea ranges between 60 and 73% in developed countries,[2,]and between 34 and 89.6% amongst women of ther eproductive age groupin India.[3,4]Primary dysmenorrhea is the more common type of dysmenorrhea with prevalence ranging from 25 to 90% throughout the world[5]and 70.2% in India.[6]

Primary dysmenorrhea usually begins within the first 6 to12 months after menarche,once a regular ovulatory cycle has been established[7] and can persist upto 30 years, with peak prevalence occurring in the late teens or early twenties. It includes sharp, intermittent spasms of lower abdominal or pelvic pain with or without radiation to the back or legs, experienced a few hours before and after the onset of menstruation. It is sometimes associated with nausea, vomiting, loosestool, loss of appetite, fatigue, dizziness,mood trouble, social withdrawal, etc.[8, 9] Dysmenorrhea has different detrimental effects on individuals and the community, and can lead todecreased work productivity and work quality, interference with daily living activities,limitationin socialization and absenteeism in school. Even if dysmenorrhea disturbs day-to-day activities,there is unawareness about its management among females.Dysmenorrhea poses a unique challenge to outcome research in homeopathy, as conventional drugs like NSAIDS havea failure rate of 20-25% along with sideeffects.[1, 10]

Primary dysmenorrhea may manifest as a single symptom, but its management has to bemultipronged, considering its

multifactorial causations. Homeopathy focuses on the complete well-being of a patient, rather than the removal of the most trouble some complaints only. Clinical evidence shows that individualized homeopathic medicines (IHMs) can be used effectively in the management of dysmenorrhea;[11] however, double-blind randomized trials have remained contradictory in conclusion. [12, 13]Different homeopathic literature and case reports revealed *Magnesiumphosphoricum*(MP) as "the great anti-spasmodic remedy" and claimed potential in lowering pain of dysmenorrhea, specifically in 6X potency.[14,15]

Thus,we hypothesized that MP 6X might be non-inferior to IHMs in the treatment of primary dysmenorrhea and this randomized trial was aimed to detect the differences caused by IHMs and MP 6X in pain intensity of dysmenorrhea after an intervention of 3 months.

Methods

Trial design: This open-label, randomized, pragmatic, two parallel arms, equivalence (non-inferiority) pilot trial was conducted at the obstetrics and gynecology out-patient department of The Calcutta Homeopathic Medical College and Hospital (CHMC&H), Kolkata, India from 15th December 2018 to 15th May 2019. The study protocol was approved *post hoc* by the Institutional Ethical Committee (IEC) (Ref. No.CHMCH/IEC/19/2018). The trial protocol and full project report were submitted to Central Council for Research in Homoeopathy, Ministry of AYUSH, Govt. of India under its Short-TermStudentship (STSH) program, 2018-19.

Participants: Inclusion criteria were the female patients who had at least 6 menstrual cycles and suffering from spasmodic pain of sufficient magnitude during menses without any diagnosed ovarian or uterine pathology (primary dysmenorrhea; ICD-10 code N94.4), aged between 12 and 30 years, symptomatic for at least 3 months, literate patients with the ability to read Bengali and/or English, and patients willing to take part in the study and giving written consent. Exclusion criteria were the patients having unevaluated gynecological abnormalities; e.g.,unexplained vaginal bleeding, cervicaldysplasia, pelvicinflammatory diseases within one month, genito-urinary tract malignancy or secondary dysmenorrhea, usingoral contraceptive pills or intra-uterine contraceptive devices inserted, diagnosed cases of unstable psychiatric illness or other systemic disease or life-threatening infections or any vital organ failure, currently receiving homeopathic treatment for a chronic condition(s) in the last 3 months, pregnant, puerperal and lactating women and substance abuse and/or dependence.

Intervention:

1. **Experimental/verum :** MP6X2-4 tablets in individualized doses (3-5 times/day for 2-4 days) withahalf cup of lukewarm water orally, every cycle for 3 months.
2. **Control:** Control was planned as administering IHMs in centesimal potencies, as decided appropriate to the case or condition. The most frequently used medicines in the first prescription in the IHMs group were *Natrum muriaticum*, *Pulsatillanigricans*, *Nitricumacidum*, *Sepia officinalis*, *Sulphur*, and *Calcareacarbonica*. Eachdose consisted of a single drop of the indicated medicine (preserved in 90% v/v ethanol) in 5 ml of distilled water, to be taken orally; dosage and repetition depended upon the individual requirement of the cases. The medicines were obtained from a Good Manufacturing Practice (GMP)

certified firm. Each dose was instructed to be taken orally on a clean tongue with an empty stomach. The duration of therapy was 3 months. Participants were assessed by the three homeopaths every month in every follow-up. Single individualized medicine was prescribed on each occasion taking into account presenting symptom totality, clinical history details, constitutional features, miasmatic expressions, and consensus among three homeopaths. The dose was also individualized and was based on the homeopaths' judgment of susceptibility and consensus.Different repertories were consulted for different cases as per the appropriateness of philosophical backgrounds, plans, and constructions. Subsequent prescriptions were generated as per Kent's observations and Hering's law. Medicine was selected on each occasion by two homeopaths, and in case of any differences in opinion, it was resolved by the involvement of the other. However, irrespective of codes, we kept provisions to prescribe different 'acute medicines' (rescue remedies) based on 'acute totality' [16] to encounter any adverse or serious adverse events, if any, as per homeopathic principles. Two of the prescribers possessed master's degrees in homeopathy with more than 20 years of experience practicing classical homeopathy. All the homeopaths involved were affiliated with respective state councils.

3. **Concomitant care:** All the participants were advised with stretching exercises and hot fomentations over the pelvic region during the cycles.

Outcome measures:

a) Primary: 0-10 numerical rating scale (NRS) measuring the intensity of pain [17] during the first two days of menstruation.

b) Secondary:Verbal Multidimensional Scoring System (VMSS) for assessment of dysmenorrheaseverity and associated symptoms [18]– consisting of questions related to physical symptoms (19 questions), psychological symptoms (6 questions), and social symptoms (5 questions), depending upon the intensity of the symptoms, 3 for maximum and 0 for its absence.

Timelines: Pain NRS was measured during the menstrual period on the 1st and 2nd day at baseline, and similarly every month up to 3 months. VMSS was measured at baseline and 3rd month.

Sample size: A prefixed margin of non-inferiority (Δ) of 1.0 was based on an assumption owing to the absence of any relevant paper of similar design; therefore, formal sample size calculation was not possible. The non-inferiority analysis included all the randomized patients using intentions-to-treat (ITT; n=60) analyses.

Randomization: Intervention (MP 6X) or comparator (IHMs) was allocated as per the random number chart generated by using the StatTrek random number generator. The chart was generated using 6 permuted blocks of size 10 to maintain equal distribution between groups and a 1:1 ratio easily.

Blinding: The treating physicians and the patients – both were aware (i.e., open-label) of the generated allocation codes throughout the study. Allocated codes were maintained till the end of the trial. The random number chart was available to the physician and also to the pharmacist, who was responsible for dispensing either MP 6Xor IHMs to the patients according to the chart.

Allocation concealment: No concealment was done; allocation was accomplished by an open list of random numbers specifying allocation as per enrolment numbers.

Ethical standards: Before enrolment, each patient was provided with a patient information sheet in local vernacular Bengali, detailing the objectives, methods, risks, and benefits of participating, and confidentiality issues. After that, written informed consent was obtained. *Post hoc* approval was obtained from the institutional ethical committee (IEC). The study was performed under the constant supervision of the IEC. The protocol conformed to the declaration of Helsinki for the ethical conduct of clinical trials involving human participants.[19]

Statistical methods: The statistical analysis followed the ITT approach. Missing values were replaced by regression to means. Bothdescriptive and inferential statistics were applied. The baseline comparability of the groups was tested using independent *t*-tests or chi-squared tests. Differences at baseline were adjusted using analysis of covariance (ANCOVA) models. Intra-group changes at different time points were tested using paired *t*-tests and one-way repeated measure analysis of variance (ANOVA). Group differences after 3 months were detected using unpaired *t*-tests at different time points. Non-inferiority of MP 6X against IHMs was accepted at alpha = 5% if the lower limit of the 95% confidence interval (CI) around the difference of the primary outcome measure was situated below the limit of non-inferiority. Non-inferiority was defined as the situation where the difference between the means was not less than -1.0. Non-inferiority might be demonstrated either by showing that the 95% confidence bound satisfied the constraint or by running a one-sided *t*-test. When using the test procedure, non-inferiority might only be asserted if the *P* value was less than 0.05. Two sample variances were pooled to estimate the standard error. SPSS® -IBM® v.20 and Stat GraphicsCenturionv.19® for Windowswere used for the statistical analysis of data.

Reporting of adverse events: The investigators had instructed the patients to report any harm, unintended effect, serious adverse event, and undue aggravation; either directly in the out-patient departments or over the phone during the trial.

Trial reporting: Reporting adhered to the CONSORT extension for non-inferiority trials [20]and RedHot guidelines for reporting homeopathy trials.[21]

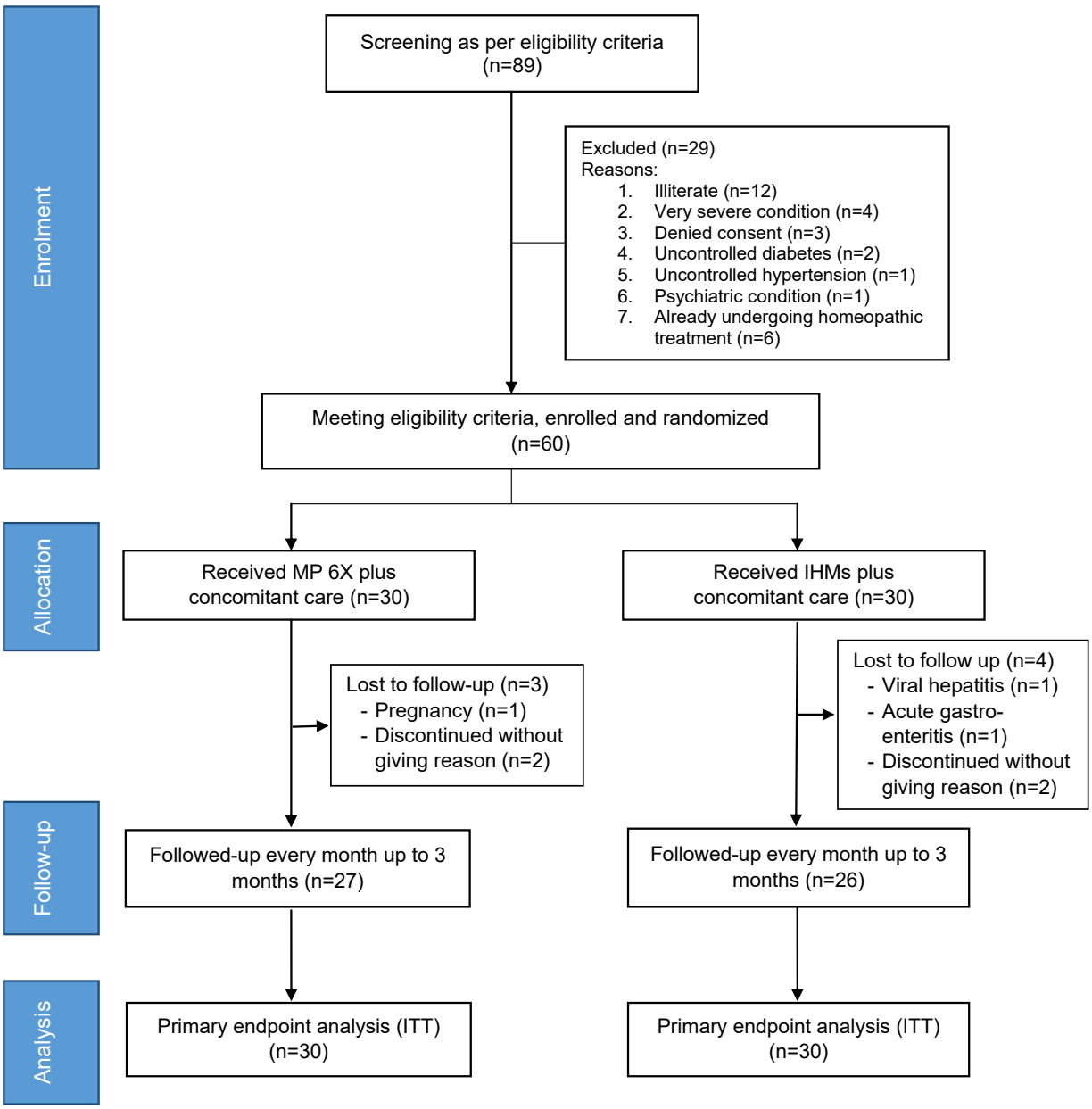
Results

Participant flow: As per the pre-specified eligibility criteria, 89 patients suffering from primary dysmenorrhea were screened; 29 were excluded on account of various reasons; 60 met the eligibility criteria and were enrolled in the trial. Following that, baseline socio-demographic and outcome data were obtained and were randomized to either MP 6Xplus concomitant care (n=30) or IHMs plus concomitant care (n=30). Outcome data were recorded every month for up to 3 months. During the intervention, 7 dropped out (3 in the MP 6X group and 4 in the IHMs group); 53 completed the trial. All the randomized participants (n=60) wereentered into the analysis. (**Figure 1:** Study flow diagram)

Recruitment: Starting from November 2018 until February 2019, a total of 60 participants were enrolled in the study.The follow-up of the last enrolled patient was completed by May 2019.

Baseline data: Different variables were studied across thetwo treatment groups – age, body mass index (BMI), residence, socio-economic status, educational status, marital status, occupation, history of dysmenorrhea in the family, and menstrual history including cycle regularity, duration, flow duration, number of pads used, the character of flow, the color of blood, character of pain, inter-menstrual events and pain in body parts. There was nostatistically significant difference in the distribution of

Fig. 1: Study flow diagram



Abbreviations: MP = *Magnesium phosphoricum*; IHMs = Individualized homeopathic medicines; ITT = Intention-to-treat

any of the variables between the two groups (all $P > 0.05$; **Table 1**), except marital status (P=0.024) and cycle irregularity (P=0.009). The distribution of the baseline outcome measures was also similar between the two groups withoutany significant group differences (all $P > 0.05$). (**Table 1**)

Numbers analyzed: Outcomes from 27/30 and 26/30 patients from the MP 6X and IHMs groups were complete respectively; the rest dropped out of the trial. All the randomized participants(n=60) entered into the final analyses.

Outcomes and estimation (ITT analysis):

- **Group differences:**

a) Reductions achieved in pain NRS on day 1 and day 2 of every month up to 3 months were statistically significant (all $P<0.05$, paired t-tests and one-way repeated measure ANOVA) in both the groups, but the reductions were significantly higher (unpaired t-tests) in the IHM group than MP 6X group at all time points:

Table 1: Comparison of baseline features between groups at baseline (N=60)

Features	MP 6X (n=30)	IHMs (n=30)	P
Age (years) [a]	18.5 (3.5)	19.1 (4.3)	0.579
Body mass index [a]	20.6 (2.9)	20.7 (3.9)	0.877
Residence [b]			0.226
▪ Urban	15	19	
▪ Semi-urban	3	5	
▪ Rural	12	6	
Socio-economic status [b]			0.285
▪ Upper	1	1	
▪ Middle	10	16	
▪ Lowe middle	19	13	
Education [b]			0.893
▪ 8th std. or below	8	8	
▪ 9th to 12th std.	19	20	
▪ Higher than 12th std.	3	2	
Marital status [b]			0.024*
▪ Single	25	17	
▪ Married	5	13	
Occupation [b]			0.711
▪ Student	18	16	
▪ Business	3	2	
▪ Service	1	3	
▪ Unemployed and housewife	8	9	
History of dysmenorrhea in family [b]	17	13	0.302

Features	MP 6X (n=30)	IHMs (n=30)	P
Menstrual history			
▪ Cycle regular [b]	22	12	0.009*
▪ Cycle duration (days) [a]	30.5 (4.9)	28.5 (5.3)	0.134
▪ Flow duration (days) [a]	4.8 (1.1)	4.8 (1.2)	0.912
▪ No. of pads used [a]	3.7 (1.1)	3.2 (1.0)	0.104
▪ Character of flow [b]			0.920
a) Fluid	5	6	
b) Partly clotted	18	18	
c) Clotted	7	6	
▪ Color of blood [b]			0.739
a) Bright red	17	13	
b) Dark red	9	13	
c) Light red	3	3	
d) Pale	1	1	
▪ Character of pain [b]			0.695
a) Cramping	14	14	
b) Pressing	3	2	
c) Pricking	0	5	
d) Colicky	3	0	
e) Dull	0	2	
f) Shooting	5	3	
g) Stabbing	1	1	
h) Piercing/stitching	2	0	
i) Bearing	1	0	
j) Cutting	1	3	
▪ Inter-menstrual events [b]			0.708
a) None	19	13	
b) Abnormal vaginal discharge	7	10	
c) Mastalgia	1	2	
d) Nausea	1	0	
e) Spotting	0	4	
f) Pain abdomen	1	0	
g) Pruritus vulvae	1	1	
▪ Pain in body parts [b]			0.634
a) Lower abdomen	12	9	
b) Lower abdomen, back	2	5	
c) Lower abdomen, back, legs	13	13	
d) Lower abdomen, legs	3	3	

Features	MP 6X (n=30)	IHMs (n=30)	P
Outcome measures [a]			
▪ Pain VAS			
a) Day 1	6.7 (1.4)	6.9 (1.0)	0.531
b) Day 2	4.9 (1.9)	4.7 (2.0)	0.699
▪ VMSS			
a) Total	26.3 (5.7)	28.1 (6.4)	0.263
b) Physical	13.6 (4.1)	15.7 (5.7)	0.105
c) Psychological	7.2 (2.0)	6.8 (2.7)	0.585
d) Social	5.6 (2.1)	6.3 (2.6)	0.278

[a] Continuous data expressed as mean (standard deviation), unpaired *t*-tests; [b] Categorical data expressed as absolute values, chi-squared test; **P* values less than 0.05 two-tailed considered as statistically significant; IHMs: Individualized homeopathic medicines; MP: *Magnesium phosphoricum*; VAS: Visual analogue scale; VMSS: Verbal Multidimensional Scoring System

day 1 ($P_{0\text{-}1}$=0.007, $P_{0\text{-}2}$=0.0004, $P_{0\text{-}3}$=0.0001) and day 2 ($P_{0\text{-}2}$=0.004, $P_{0\text{-}3}$=0.020), except day 2 of 1st month ($P_{0\text{-}1}$=0.350); thereby suggesting statistically significant advantages in the IHMs group against MP 6X group in reduction of pain NRS. **(Table 2**; **Figures 2, 3)**

b) Similarly, intra-group reductions achieved and group differences detected on VMSS total and subscale scores were alsosignificantlyhigher in the IHMs group than the MP 6X group; thus, favoring the former against the latter [total $P_{0\text{-}3}$=0.0001, physical $P_{0\text{-}3}$=0.0001, psychological $P_{0\text{-}3}$=0.0001, and social $P_{0\text{-}3}$=0.001] (all *P*=0.001). (**Table 2**; **Figures 4-7**)

- **Equivalence statistics:** Although the reductions achieved in the MP 6X group were lower than the IHMs group, still, non-inferiority was demonstrated by MP 6X against IHMs in pain NRS on the 1st day of menstrual flow after 3 months of intervention [mean difference=2.0, SE=0.5, lower 95% confidence limit 1.1, *t*=5.871, *P*<0.001; **Figure 8**], on the 2nd day [mean difference=1.3, SE=0.5, lower 95% confidence limit 0.5, *t*=4.730, *P*<0.001; **Figure 9**] and in VMSS total scores [mean difference=11.6, SE=2.0, lower 95% confidence limit 8.3, *t*=6.333, *P*<0.001; **Figure 10**].

Adverse events: No adverse were reported during the trial that can be attributed causally to either of the interventions.

Discussion

An open-label, randomized, pragmatic, non-inferiority, pilot trialwas performed on 60females suffering from primary dysmenorrhea at CHMC&H, Kolkata. Improvement in pain NRS on the 1st and 2nd days of menstruation and VMSS total and subscale scores was significantly higher in the IHMs group than the MP 6X group; still, non-inferiority was revealed by MP 6X against IHMs. With the trial design being pilot, no definite conclusion could be arrived at regarding the non-inferiority of MP 6X against IHMs. Further exploration of similar and robust designs is warranted.

Table 2: Intra-group changes and inter-group differences in outcomes in the two groups (adjusted for baseline differences by ANCOVA model); ITT analysis (N=60)

Outcomes	Baseline: Mean (SE)	Mo 1: Mean (SE)	Mo 2: Mean (SE)	Mo 3: Mean (SE)	Changes Mo 0-1: Mean (95% CI)	Changes Mo 0-2: Mean (95% CI)	Changes Mo 0-3: Mean (95% CI)	Gr. diff. Mo 0-1: Mean (95% CI)	Gr. diff. Mo 0-2: Mean (95% CI)	Gr. diff. Mo 0-3: Mean (95% CI)
IHMs group (n=30)										
1. Pain VAS										
a) Day 1	6.9 (0.2)	5.0 (0.2)	4.2 (0.2)	3.2 (0.3)	2.2 (1.7, 2.7) [a]	2.9 (2.3, 3.6) [a']	3.7 (2.9, 4.5) [a", a'"]	1.0 (0.3, 1.7) *	1.6 (0.8, 2.4) *	2.2 (1.2, 3.2) *
b) Day 2	4.7 (0.4)	3.2 (0.3)	2.6 (0.3)	2.2 (0.3)	1.5 (0.9, 2.1) [b]	2.1 (1.5, 2.8) [b']	2.6 (1.7, 3.5) [b", b'"]	0.4 (-0.4, 1.2) [ns]	0.9 (0.1, 1.7) *	1.2 (0.2, 2.2) *
2. VMSS										
a) Total	28.1 (1.2)	--	--	12.4 (1.5)	--	--	15.7 (11.9, 19.6) [c]	--	--	13.3 (9.2, 17.4) *
b) Physical	15.7 (1.0)	--	--	6.9 (0.8)	--	--	8.8 (6.2, 11.4) [d]	--	--	8.0 (5.3, 10.7) *
c) Psychological	6.8 (0.5)	--	--	3.2 (0.6)	--	--	3.7 (2.7, 4.6) [e]	--	--	3.0 (1.8, 4.2) *
d) Social	6.3 (0.5)	--	--	2.3 (0.4)	--	--	4.0 (2.8, 5.1) [f]	--	--	3.1 (1.8, 4.4) *
MP 6X group (n=30)										
1. Pain VAS										
a) Day 1	6.7 (0.2)	5.8 (0.3)	5.7 (0.3)	5.2 (0.4)	1.2 (0.6, 1.7) [g]	1.3 (0.6, 1.9) [g']	1.5 (0.9, 2.2) [g", g'"]			
b) Day 2	4.9 (0.4)	3.9 (0.4)	3.7 (0.4)	3.5 (0.4)	1.1 (0.5, 1.6) [h]	1.2 (0.6, 1.8) [h']	1.4 (0.8, 2.1) [h", h'"]			
2. VMSS										
a) Total	26.3 (1.0)	--	--	24.0 (1.2)	--	--	2.4 (0.8, 3.9) [i]			
b) Physical	13.6 (0.8)	--	--	12.8 (0.7)	--	--	0.8 (0.1, 1.5) [j]			
c) Psychological	7.2 (0.4)	--	--	6.5 (0.4)	--	--	0.7 (0.2, 1.2) [k]			
d) Social	5.6 (0.4)	--	--	4.7 (0.5)	--	--	0.9 (0.3, 1.5) [l]			

Intra-group changes (IHMs):

a) Pain VAS Day 1: [a] $t29 = 9.251$, $P < 0.001$, paired t-test; [a'] $t29 = 8.234$, $P < 0.001$, paired t-test; [a"] $t29 = 8.902$, $P < 0.001$, paired t-test; [a'"] Wilks' $\lambda = 0.202$, partial $\eta^2 = 0.798$, $F3, 27 = 35.453$, $P < 0.001$, one-way repeated measure ANOVA

b) Pain VAS Day 2: [b] $t29 = 5.642$, $P < 0.001$, paired t-test; [b'] $t29 = 6.509$, $P < 0.001$, paired t-test; [b"] $t29 = 5.621$, $P < 0.001$, paired t-test; [b'"] Wilks' $\lambda = 0.398$, partial $\eta^2 = 0.602$, $F3, 27 = 13.627$, $P < 0.001$, one-way repeated measure ANOVA

c) VMSS total: [c] $t29 = 8.116$, $P < 0.001$, paired t-test

d) VMSS physical: [d] $t29 = 6.507$, $P < 0.001$, paired t-test

e) VMSS psychological: [e] $t29 = 7.281$, $P < 0.001$, paired t-test

f) VMSS social: [f] $t29 = 6.980$, $P < 0.001$, paired t-test

Intra-group changes (MP 6X):

g) Pain VAS Day 1: [g] $t29 = 4.642$, $P < 0.001$, paired t-test; [g'] $t29 = 4.136$, $P < 0.001$, paired t-test; [g"] $t29 = 4.678$, $P < 0.001$, paired t-test; [g'"] Wilks' $\lambda = 0.502$, partial $\eta^2 = 0.498$, $F3, 27 = 8.912$, $P < 0.001$, one-way repeated measure ANOVA

h) Pain VAS Day 2: [h] $t29 = 4.000$, $P < 0.001$, paired t-test; [h'] $t29 = 4.397$, $P < 0.001$, paired t-test; [h''] $t29 = 4.746$, $P < 0.001$, paired t-test; [h'''] Wilks' $\lambda = 0.555$, partial $\eta^2 = 0.445$, $F3, 27 = 7.217$, $P < 0.001$, one-way repeated measure ANOVA

i) VMSS total: [i] $t29 = 3.106$, $P = 0.004$, paired t-test

j) VMSS physical: [j] $t29 = 2.340$, $P = 0.026$, paired t-test

k) VMSS psychological: [k] $t29 = 2.616$, $P = 0.014$, paired t-test

l) VMSS social: [l] $t29 = 2.992$, $P = 0.006$, paired t-test

Group differences: IHMs vs. MP 6X (unpaired t-tests)

m) Pain VAS Day 1 Month 1: $t58 = 2.774$, $P = 0.007$; month 2: $t58 = 3.771$, $P = 0.0004$; month 3 $t58 = 4.400$, $P = 0.0001$

n) Pain VAS Day 2 Month 1: $t58 = 0.943$, $P = 0.350$; month 2: $t58 = 2.121$, $P = 0.004$; month 3 $t58 = 2.400$, $P = 0.020$

o) VMSS total month 3: $t58 = 6.451$, $P = 0.0001$

p) VMSS physical month 3: $t58 = 5.996$, $P = 0.0001$

q) VMSS psychological month 3: $t58 = 5.145$, $P = 0.0001$

r) VMSS social month 3: $t58 = 4.621$, $P = 0.001$

SE = standard error; CI = confidence interval; VMSS: Verbal Multidimensional Scoring System; ns = non-significant

Table 3: Indicated medicines in the IHMs group at baseline (n=30)

Name of the medicines	Frequency	Percentage
1. Calcarea carbonica	2	6.7
2. Calcarea phosphorica	1	3.3
3. Graphites	1	3.3
4. Ignatia amara	2	6.7
5. Natrum muriaticum	6	20
6. Nitricum acidum	3	10
7. Pulsatilla nigricans	5	16.7
8. Phytolacca decandra	1	3.3
9. Sanguinaria canadensis	1	3.3
10. Sepia officinalis	3	10
11. Silicea terra	1	3.3
12. Sulphur	3	10
13. Viburnum opulus	1	3.3

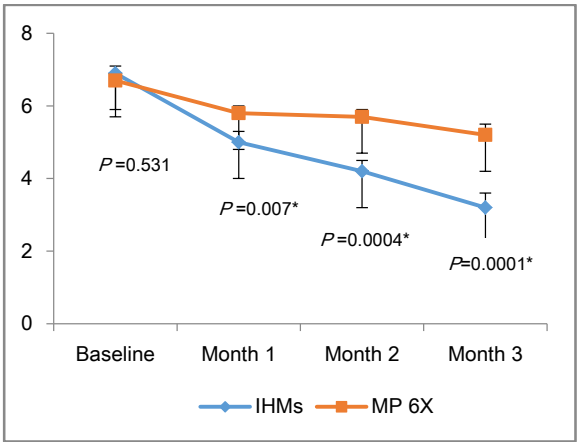


Figure 2: Changes in pain VAS on day 1 over 3 months in the two groups

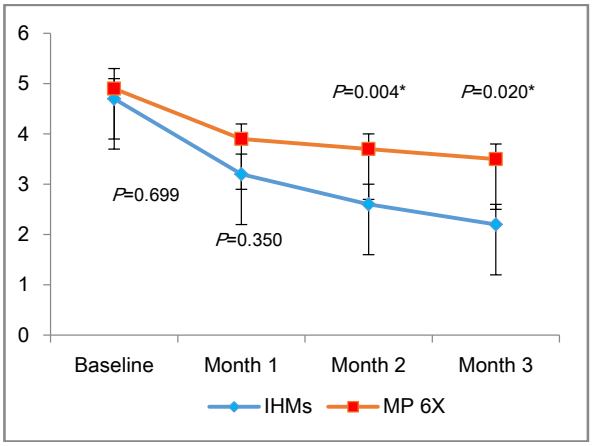


Figure 3: Changes in pain VAS on day 2 over 3 months in the two groups

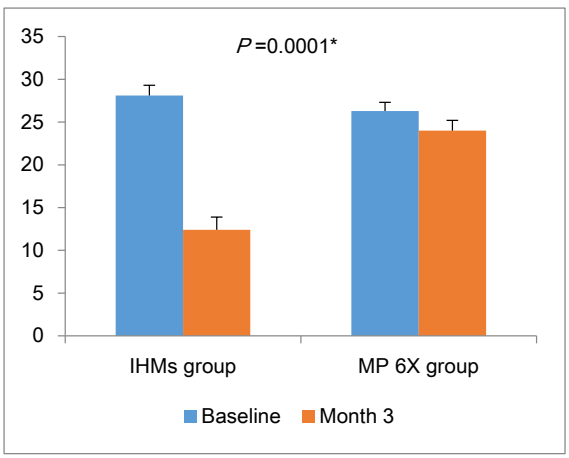


Figure 4: Changes in VMSS total score over 3 months in the two groups

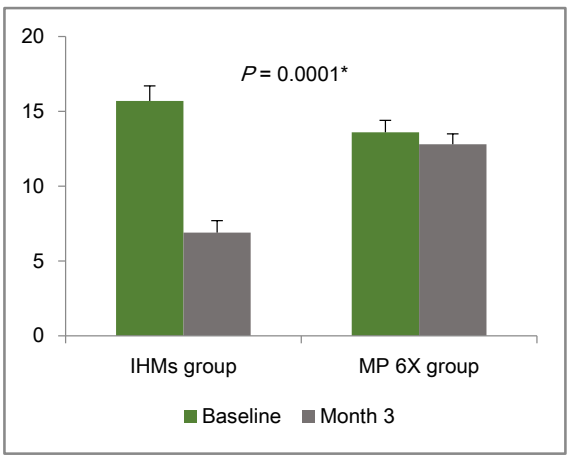


Figure 5: Changes in VMSS physical score over 3 months in the two groups

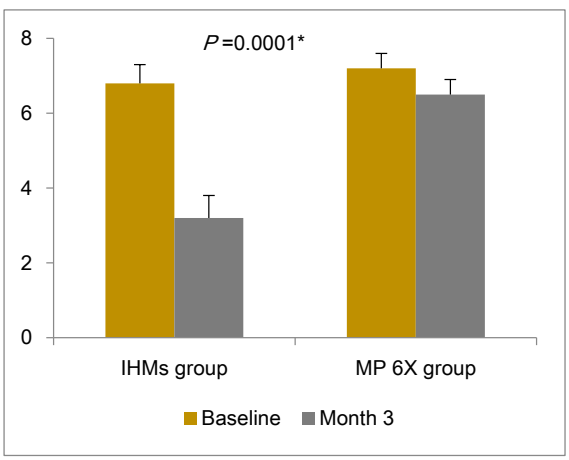


Figure 6: Changes in VMSS psychological score over 3 months in the two groups

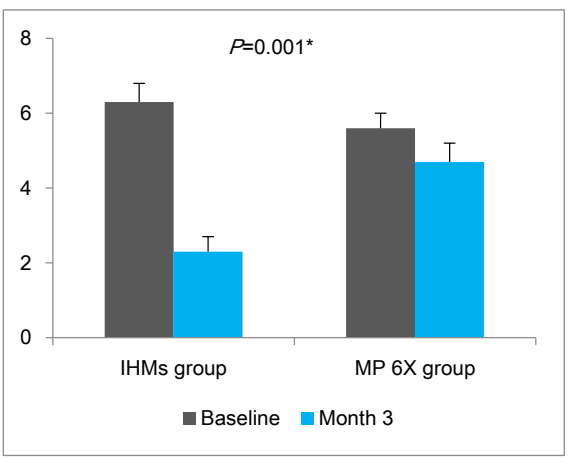


Figure 7: Changes in VMSS social score over 3 months in the two groups

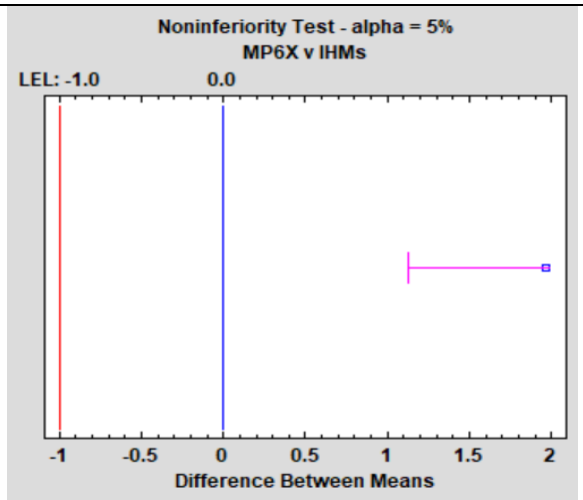


Fig. 8: Non-inferiority demonstrated by MP 6X against IHMs in pain NRS on day 1 of menstrual flow after 3 months of intervention

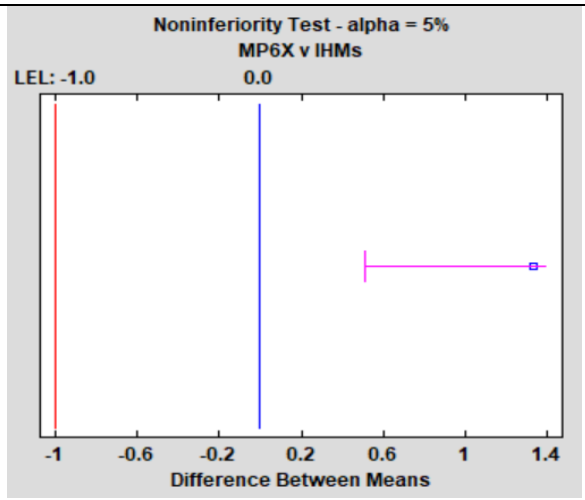


Fig. 9: Non-inferiority demonstrated by MP 6X against IHMs in pain NRS on day 2 of menstrual flow after 3 months of intervention

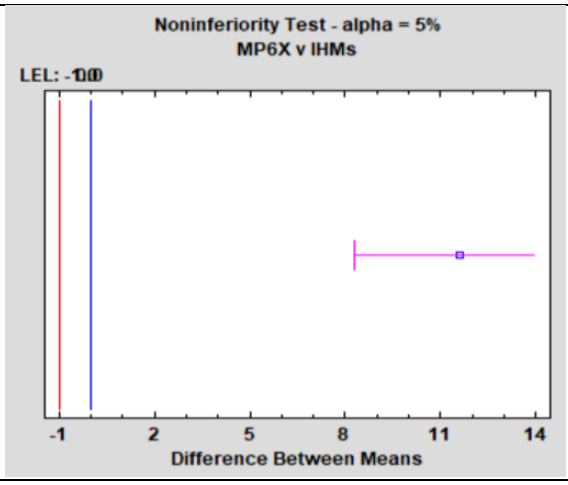


Fig. 10: Non-inferiority demonstrated by MP 6X against IHMs in VMSS total score after 3 months of intervention

The major strengths of the study were its randomized and pragmatic nature and ITT analysis. The baseline differences betweenthetwo trial arms were adjusted using ANCOVA models; thus, ensuring comparability. ITT analysis allowed all the randomized patients to enter into the final analysis by the imputation of the missing values. The use of multiple outcome measures has made the study findings robust and generalizable. No placebo control was used; rather all the randomized participants received active interventions – either MP 6X or IHMs. Hence, ethical concerns were comparatively less than in conducting placebo-controlled trials. We planned for the detection of group differences and non-inferiority statistics as well.

Trial recruitment was fluent owing to a systematic recruitment strategy and adequate referrals from colleagues and other outpatient departments. The authors took additional measures to improve trial recruitment, including verbal reminders to each attending physician, regular WhatsApp group message reminders during clinical hours, and posters in waiting areas and on walls of outpatient departments. The study was the very first of its kind in homeopathy; hence exploratory. Effect size could not be calculated on account of the absence of any study of similar design; hence formal sample size calculation was also not possible and was based on assumption. The trial was open; no blinding was used – thus, the trial was subjected to performance bias and

detection bias. However, this could have been tackled by a double-dummy design, which would not affect the pragmatic nature of the trial. Another important limitation was that only verbal compliance to the advised interventions could be assured in our study; still, compliance bias, if any, randomization would have mitigated the effects mutually in both groups. Future trials should keep provisions for assessing non-adherence more robustly.

Used medicines in the IHMs group were quite similar to those used by Ghosh, *et al*.[13] and as referred to in homeopathy literature.[14, 15] Dr. Kent has also mentioned the role of MP in menstrual neuralgia.[22] Homeopathic repertories mention *Calcareacarbonica*, *Calcareaphosphorica,* and *Pulsatillanigricans* in higher grades in the treatment of dysmenorrhea.[23-25] A prospective, multicentric, observational study revealed significant improvement with homeopathic treatment in dysmenorrhea.[11] A clinical trial conducted at the OPD of Central Research Institute of Homoeopathy, Calcutta showed that homeopathic medicines *Viburnum opulus* and *Xanthoxylumamericanum* produced statistically significant improvements in symptom complex associated with dysmenorrhea.[26] The medicine *Viburnum opulus* was also used in our trial, but in a single case in the IHMs group. It was also used by Ghosh, et al.[13] The number of participants enrolled by us (n=60) was much less than that by Ghosh, *et al*(n=128),[13] adopted a different design with different experimental intervention and comparator arms. The outcome measures were the same – pain NRS and VMSS and the measurement timelines were also the same – at baseline and every month for up to 3 months.

Larger and definitive trials should be taken up to address the non-inferiority of MP 6X against IHMs, preferably in multicenter approaches to enhance the validity of the findings. Future trials should also aim at exploring the effectiveness of MP 6X and IHMs in pragmatic design against standard care.

Conclusion

In an open, randomized, pragmatic, non-inferioritypilottrialinvolving 60females suffering from primary dysmenorrhea at CHMC&H, Kolkata, reductions achieved in pain NRS on the 1st and 2nd days of menstruation and VMSS total and subscale scores were significantly higher in the IHMs group than the MP 6X group; still, non-inferiority could be demonstrated by MP 6X against IHMs. The trial being preliminary and exploratory, no inference could be drawn regarding the non-inferiority of MP 6X against IHMs.Larger independent replications in robust design are warranted.

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