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Potentized, oral preparation of Capsaicin alkaloids and magnesium phosphoricum in treatment of chronic pain: A clinical trial

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Abstract

A double blind, randomized, comparative study to evaluate efficacy and safety of CP with MP was conducted in 116 patients having sub-acute and chronic painful conditions by evaluating for intensity measured on Numeric Rating Scale. Out of 116 patients, 72 (62.07%) have shown improvement (30.92%) in pain. Subgroup analysis, in CP group showed higher reduction in intensity of pain (p=0.026) in age group 18-30 years and in patients with LS spine pain (p=0.014). Higher rate of change in stiffness was statistically significant (p=0.030). Patients with limb/heel/ankle pain reported reduction in the swelling of joint. Rate of reduction in tenderness in knee (p=0.014) and rate of decrease in sleep interference (p=0.015) was higher in the age group of 31-50 years. Patients on MP showed reduction in knee pain (p=0.014) and joint swelling (p=0.034). Reduction in tenderness (p=0.038) in weight group of 61-90 kg and the intensity of pain (p=0.018) in age group of 51-80 years was observed. The Law of Similars was investigated using pain producing Capsaicin alkaloids in extremely diluted dose. Ultra-molecular, highly diluted (potentized) Capsaicin alkaloids and Magnesium Phosphoricum were found effective and safe in reducing the intensity of pain.

Keywords: Capsaicin, Dihydrocapsaicin, Magnesium Phosphoricum, clinical trial, pain, chronic pain, potentization, ultra-dilute dose, homeopathy, Law of Similars, randomization, ethics, safety

Introduction

Chronic pain is defined as one that extends beyond the expected period of healing (1), which remains a challenge in medical practice. The extremely diluted (potentized) homeopathic medicines are administered in 30c, 200c (or more) potencies. 1c potency is made by making a solution of one part of drug substance mixed with 99 parts of vehicle (1-2) (generally, alcohol), which undergoes rigorous succussions.

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One part of 1c is again mixed with 99 parts of vehicle to repeat the process, to arrive to 2c (10^{-4}), and likewise 3c, 4c, …., 30c (1^{-60}), etc. are prepared.

Extreme potentized dilutions have shown to retain starting material in the form of nanoparticles (2). Clinical efficacy of potentized preparations in pain management has been shown in several clinical studies (3-6). Some in the past has questioned efficacy of the micro-dose of homeopathic medicine (7). The Law of Similars, the fundamental homeopathic principle, which states that any substance, which has a capacity to produce symptoms in humans, also has the capacity to reduce similar symptoms, if administered in very small dose (8).

Capsaicin and Dihydrocapsaicin are known pain-producing agents. Capsaicin is conventionally used as an ointment and dermal patch to treat certain painful conditions (9). However, its use by oral administration in clinical practice is not known. Applying the principle of Law of Similars, the investigator has experimented with oral use of potentized, ultra-dose for painful conditions to examine two concepts: 1) If the observation could support the Law of Similars and 2) If extremely diluted dose has any therapeutic action.

Objectives

Primary objective of this study was to evaluate the efficacy of potentized preparation CP-30c potency by measuring the reduction in intensity of pain using Numeric rating scale (NRS).

Secondary objectives of this study includes assessment of efficacy by using Clinical Global Impression (CGI) scale, effect of pain on sleep, need of rescue medication, effect on vital signs as well as on laboratory parameters. Also, include evaluation of changes in symptoms such as stiffness, joint swelling, tenderness and redness by using five points rating scale (very severe, severe, moderate, mild, none for the pain), time needed for the participants to be symptoms free, duration of relief and adverse events experienced by participants.

Use of CP in potentized preparation in pain management would also support Law of Similars.

Methods

This was the single center randomized, double blind comparative clinical study of two homeopathic oral preparations: 1) Combined preparation of Capsaicin and Dihydrocapsaicin 30c (CP), 2) Magnesium Phosphoricum 30c (MP). The trial was registered on Clinical Trial Registry of India (CTRI) (identifier number CTRI/2012/02/002450) (10). Ethics committee approved the study protocol. All study procedures were performed in accordance with ICH Good Clinical Practices (11) and the Ethical Guidelines for Biomedical research on Human Subjects issued by the Indian Council of Medical Research (12). Manuscript writing and data reporting have been done according to CONSORT guidelines (13).

Eligible patients were identified; written informed consent was obtained voluntarily from patient. Patients meeting all inclusion/exclusion criteria were randomized in the study. Randomization list was generated using computerized program for randomization. Total 116 patients suffering from sub-acute and chronic pain symptoms were enrolled. The patients were given two-week treatment schedule of either CP or MP; and patients were evaluated at protocol defined four visits. The patients were followed for two weeks; data was recorded in case record form as per source documents and collected data was analyzed statistically using SPSS software by independent agency. Laboratory investigations, safety and ethical measures were taken care of.

The trial was conducted at Life Force research center having a research team comprising of five staff members including four physicians and one clinical trial expert. CP (30c) was prepared by the investigator as per the Hahnemannian multi-vial dilution method and potentized up to 30 c potencies (14) and MP (30c) was procured from the market.

Patient population

Patients reported with moderate (greater than 4) to severe pain (up to 10) on Numerical Pain Rating Score scale (NRS) were considered for this study and enrolled based on following inclusion/exclusion criteria.

Inclusion criteria: Male or female patients of between 18 and 65 years of age; having moderate to severe pain (NRS > 4), experiencing any sub-acute or chronic painful condition for at least once a day, either in-spite of taking pain killer medications or without. Patients were allowed to continue the same dose (without increasing) of existing pain killer medications, if any. Patients having any sub-acute or chronic pain e.g. musculoskeletal injuries, myalgia, neck pain, limb pain, low back pain, joint pain, musculoskeletal pain, or any sub-acute painful conditions such as spondylosis (lumbar and cervical), spinal stenosis, periarthritis, frozen shoulder, prepatellar bursitis, low-back pain, tendonitis, tenosynovitis, bursitis, osteoarthritis, upper abdomen pain and neuropathy pain, cancer pain, etc. were allowed to participate in the study.

Exclusion criteria: Aimed at generating patient samples limited to the individuals with selective patient population as described above; and patients having any of the complaints of pain due to critical conditions of chronic appendicitis, cholecytisis, pancreatitis, renal colic, active rheumatoid arthritis, severe psoriatic arthritis, septic arthritis, etc.; or having uncontrolled systemic diseases like diabetes or hypertension; or patients with mentally retarded conditions; and pregnant and lactating women were excluded from the study.

Sample size was calculated based on hypothesis that, whether study medications CP-010 show at least two point reduction on numeric rating scale and how much percentage of patients shows this two point reduction on NRS. Qualified patients were screened and randomized in a 1:1 ratio to receive CP or MP as per randomization schedule (see flow chart for patient disposition). Randomization list was prepared using software. The randomization numbers were given to the patients on first come first basis. Patients and all study personnel remained blinded to the treatments throughout the study. Patients were prescribed with dose of 6 pills (pill size 30) thrice a day for two weeks. At screening visit; assessments including physical examination, vital signs, medical history, twelve-lead electrocardiogram, hematology and blood biochemistry, routine urine and pregnancy test (for childbearing female patients) were done. NRS: The 0 to 10 Numeric rating scale is commonly and successfully used in research to measure the pain intensity. CGI (Clinical Global Impression) and sleep assessments, patient daily diary, need for rescue medications were also performed.

Statistical methodologies

Independent statistician carried out data entry and the data analysis. Statistician opened blinding after database was locked. All the continuous variables were summarized using Number, Mean, Standard deviation, Median, Range, Minimum and Maximum. Counts and percentages were provided for all the categorical data. Statistical tests of hypothesis were carried out two-sided at 5% level of significance. For hypothesis testing, decision on choice of the parametric test or its non-parametric alternative was taken on the normality of the data. Descriptive Analysis, Cross Tabulation Key Findings, Pre-intervention and Post-intervention Analysis, Analysis supporting - Primary objective and secondary objectives were carried out using SPSS (Statistical Product and Service Solutions) software used for statistical analysis.

Results

Patients were uniformly distributed with respect to age and weight. Study included more females (69%) in CP and (62%) in MP. Patients were in the age range of 18 to 80 years. Mean age for cases was 43. Majority (55.2%) of study participants were in the age range 31 to 50 years. Mean weight of cases was 62 kg in CP and 63 kg in MP group. Around 70% of patient population was in the weight category of 51 to 70 kg. Study participants had normal heart rate, and blood pressure.

Efficacy in terms of percentage improvement

Out of 116 patients, 72 (62.07% population) had shown (30.92%) improvement in pain. 21 patients (18.1%) shown improvement in pain between 30 and 50%; and 10 patients (8.62%) above 50% up to 90%. Further individual patients were assessed for drug efficacy measured as 20% or 30% improvement in

patients' NRS scores at baseline and at visit 4. It is evident from the (see table 1) that 47% of patients showed 20% and 30% patients showed 30% improvement in NRS score.

Table 1. Efficacy in terms of percentage improvement, 47% of patients showed 20% and 30% patients showed 30% improvement in NRS score

All Patients	Total	Number of patients shown 20% improvement	Number of patients shown 30% improvement
CP	58	28 (48%)	17 (29%)
MP	58	27 (47%)	18 (31%)
Overall	116	55 (47%)	35 (30%)

Patients with primary complaint (N=85)

Patients with primary complaint of pain were classified into five major groups (knee pain, lumbo-sacral spine pain, back pain, limb pain, and neck pain) and some minor groups like shoulder pain, finger pain, etc. The major group comprised of 85 patients (73%) out of 116 patients. 39% of patients showed 20% and 22% patients showed 30% improvement in NRS score (see table 2).

Table 2. Efficacy in terms of percentage improvement for primary complaint major groups, knee, LS spine, back, limb/heel/ankle, neck pain

Major groups	Total number of patients	Number of patients shown 20% Improvement	Number of patients shown 30% improvement
Primary pain complaint			
CP	47	19 (40%)	12 (26%)
MP	38	14 (37%)	7 (18%)
Overall	**85**	33 (**39%**)	19 (**22%**)
Patients with knee pain			
CP	13	4 (31%)	2 (15%)
MP	7	2 (29%)	2 (29%)
Overall	**20**	6 (**30%**)	4 (**20%**)
Lumbo-sacral spine			
CP	11	3 (27%)	2 (18%)
MP	9	5 (56%)	0
Overall	**20**	8 (**40%**)	2 (**10%**)
Back Pain			
CP	4	2 (50%)	0
MP	7	3 (43%)	3 (43%)
Overall	**11**	5 (**45%**)	3 (**27%**)
Limb/ Heel/ Ankle pain			
CP	14	7 (50%)	6 (43%)
MP	9	2 (22%)	1 (11%)
Overall	**23**	9 (**39%**)	7 (**30%**)
Neck pain			
CP	5	3 (60%)	2 (40%)
MP	6	2 (33%)	1 (17%)
Overall	**11**	5 (**45%**)	3 (**27%**)

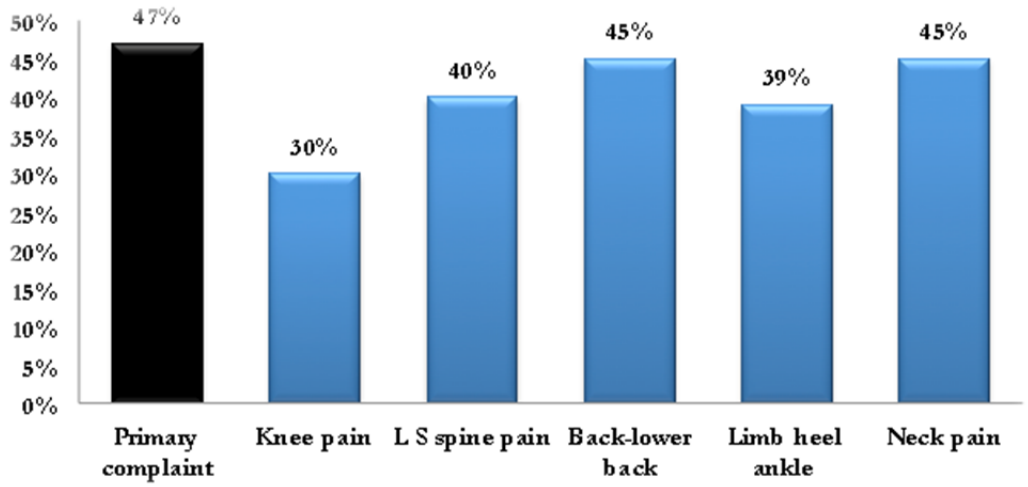

Figure 1. Number of patients shown 20 percent improvement.

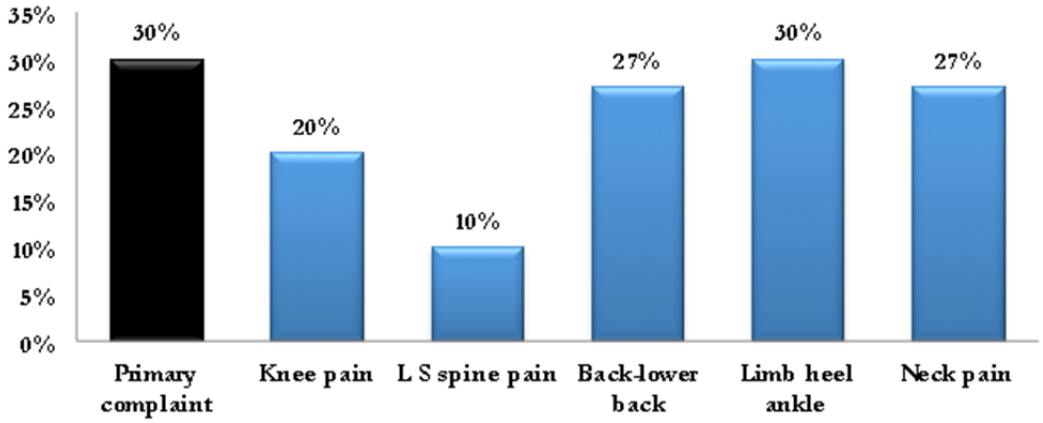

Figure 2. Number of patients shown 30 percent improvement.

Subgroup analysis for primary complaint was done, however, the sample size for such subgroup was not uniform. It is to be noted that low sample size in respective arms makes the conclusion difficult.

Out of 20 patients with knee pain, 6 patients (30%) showed 20% and 4 patients (20%) showed 30% improvement in NRS score (see figures 1, 2). Out of 20 patients with LS spine pain, 8 patients (40%) showed 20% and 2 patients (10%) showed 30% improvement in NRS score (see figures 1, 2). Out of 11 patients with Back pain, 5 patients (45%) showed 20% and 3 patients (27%)showed 30% improvement in NRS score (see figures 1, 2). Out of 23 patients with limb/heel/ankle pain, 9 patients (39%) showed 20% and 7 patients (30%) showed 30% improvement in NRS score (see figures 1, 2) and out of 11 patients with neck pain, 5 patients (45%) showed 20% and 3 patients (27%) showed 30% improvement in NRS score (see figures 1, 2).

Rate of change in numeric rating scale from baseline to visit 4 for the cases on CP in the age group of 18-30 years of age was statistically significant (p=0.026) than patients in the same age group taking MP (see figure 3). Patients in age group of 51-80 years: Rate of change in NRS score from baseline to visit 4 for the patients taking MP in the age group of 51-80 years of age was significantly (p=0.018) different from respective cases in the same age group taking CP (see figure 4). Patients on CP having lumbosacral spine pain showed statistically significant (p=0.014) reduction in intensity of their pain as compared to patients taking MP.

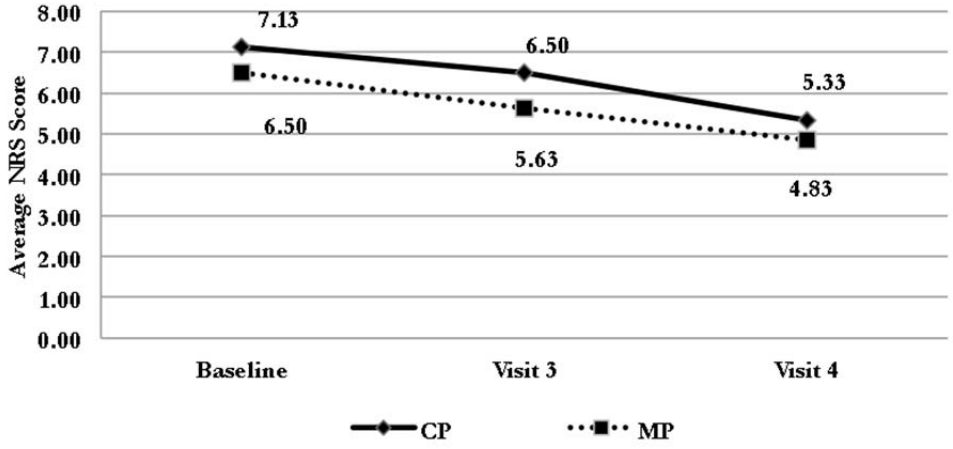

Figure 3. Change in NRS in age group 18-30 years.

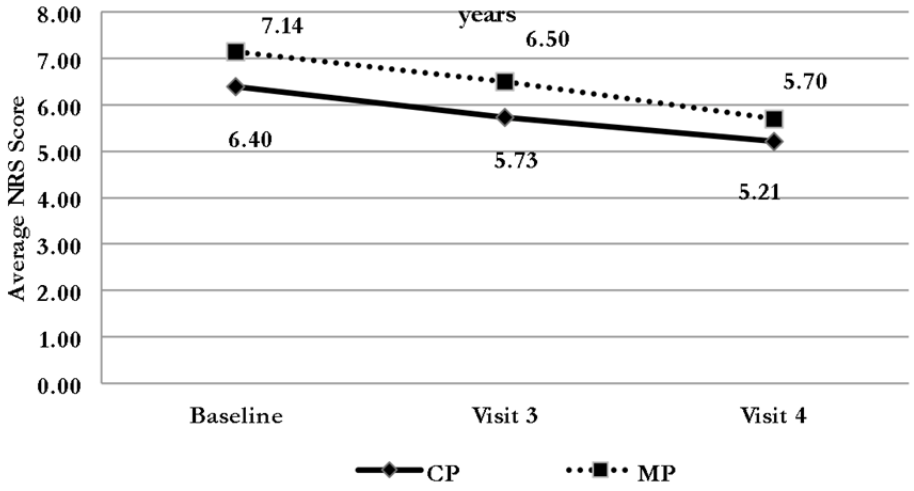

Figure 4. Change in NRS in age group 51-80 years.

Patients with knee pain, taking MP, showed statistically significant pain reduction (p=0.014) as compared to respective cases taking CP (see figures 5 and 6).

Twenty-seven (23.27%) patients were taking medication for pain management (painkillers) at the baseline, and still having pain. Out of these 19 (70%) patients had shown up to 60% improvement in terms of reduction in pain after taking the investigational products.

Twenty (17.24%) patients took rescue medication (painkiller) during the course of trial, which were not taking it at baseline. This was observed to be attributed to severity of pain, lack of expected response to IP and over exertion in those patients.

In patients taking CP (weight range 61-90 kg), the rate of change of CGI (Clinical Global Impression) was higher (p=0.035) than the patients taking MP. 4.4 Sleep interference (general)

Percentage of patients on CP reporting decrease in sleep interference (visit wise) in age group of 31-50 years was higher than those on MP, in same age category. This finding was statistically significant (p=0.015) (see figure 7).

Patients with knee pain, taking MP reported faster decrease in their sleep interferences than cases on CP. This rate of decrease in sleep interference was statistically significant (p=0.016) (see figure 8).

The rate of change of stiffness (from very severe to mild) among all cases on CP was statistically significantly higher (0.03) than the patients on MP.

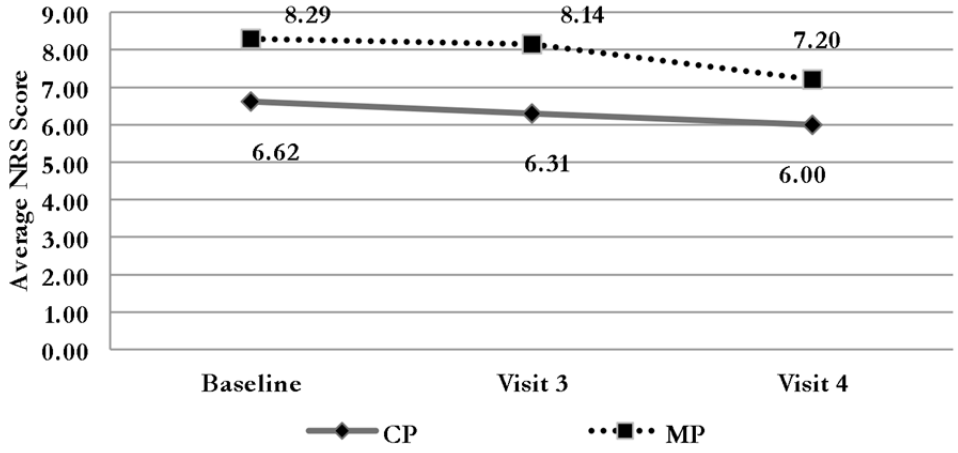

Figure 5. Change in NRS in patients with knee pain.

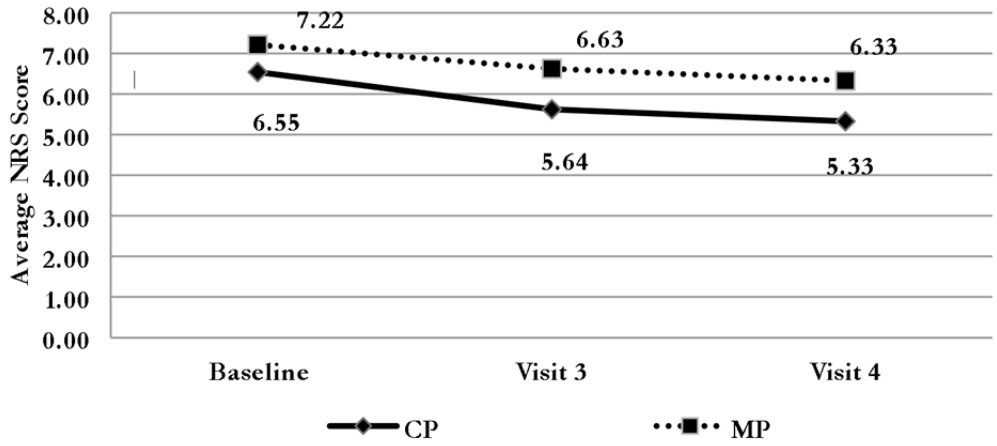

Figure 6. Change in NRS in patients with LS spine pain.

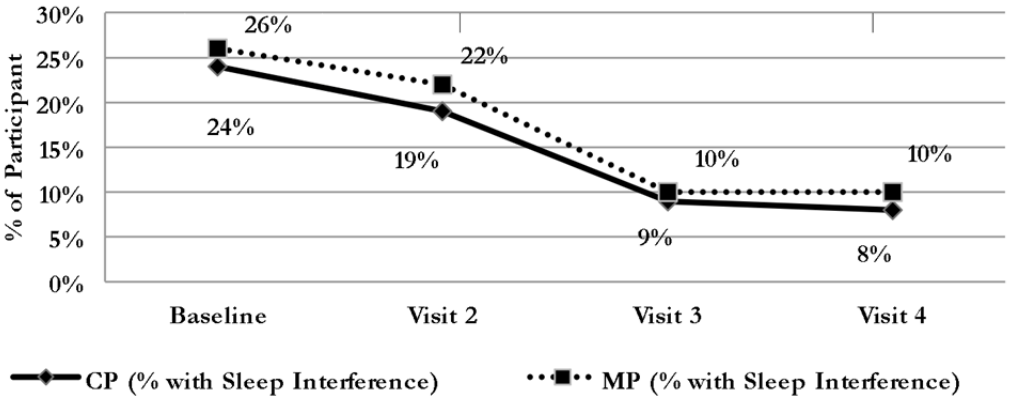

Figure 7. Sleep interference in patient's age group 31-50 years.

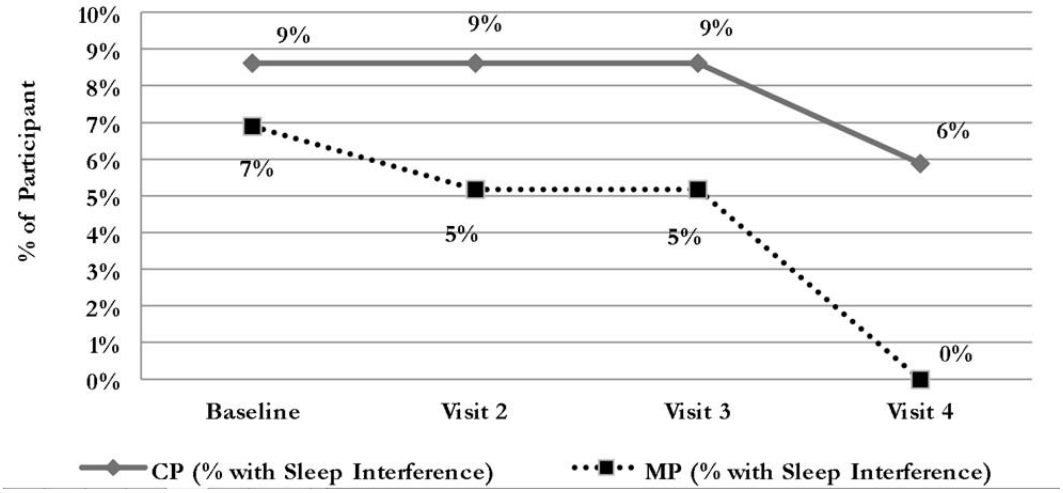

Figure 8. Sleep interference in patients with knee pain based on patient diary.

Table 3. Visit wise five point ratings for subgroup of patients taking study and comparator drugs

Subgroup of Patients	Baseline	Visit 3	Visit 4	Baseline	Visit 3	Visit 4	*p* value
	CP	CP	CP	MP	MP	MP	
Stiffness							
Overall patients	3.83	4.18	4.41	3.57	3.74	4.13	0.03
Male patients	4.06	4.22	4.44	3.64	3.73	4	0.003
Patients in age group of 31 - 50 years	3.77	4.12	4.39	3.52	3.66	4.04	0.028
Patients in age group of 51 - 80 years	3.93	4.2	4.36	3.43	3.71	4.05	0.021
Patients in weight group of 40 - 60 kg	3.77	4.19	4.53	3.46	3.63	4.09	0.026
Patients in weight group of 61 - 90 kg	3.73	3.86	4.19	3.47	3.57	4.02	0.021
Patients who took Rescue Medication	3.71	3.71	4.09	3.05	3.11	3.71	0.023
Patients with limb/ heel/ ankle pain	4.57	4.57	4.69	3.89	3.63	3.86	0.009
Swelling							
Patients in age group of 51 - 80 years	4.4	4.53	4.71	4.19	4.43	4.55	0.034
Patients with limb/heel/ankle pain	4.5	4.57	4.69	4.89	4.88	5	0.007
Tenderness							
Patients in age group of 51 - 80 years	4	4.27	4.36	4.43	4.52	4.6	0.035
Patients in weight group of 61 - 90 kg	4.21	4.24	4.57	4.35	4.5	4.73	0.038
Patients with knee pain	4.08	4.17	4.27	4.57	4.57	4.6	0.014

In the subgroup analysis, this rate of change was observed among male cases (p=0.003), older age (51to 80 years) group cases (p=0.021), patients who took MP and rescue medication (p=0.023), and patients on CP with limb/heel/ankle pain (p=0.009). Patients on MP in the age group of 51-80 years showed statistically significant reduction in their joint swelling as compared to cases from the same age group (p=0.034). Patients on CP with limb/heel/ankle pain reported statistically significant (p=0.007) reduction in joint swelling, the rate of change in tenderness in cases on CP in the age group of 51-80 years was higher (p=0.035) and with knee pain was higher (p=0.014). However, the rate of change in tenderness in patients on MP in the weight group of 61-90 kg was higher (p=0.038) than those on CP (Refer Table 3).

Percentage of patients who reported relief was calculated (difference between CP over MP) and analyzed. Relief reported by the patients (in terms

of%) was highest in the group with neck pain (22%), while patients with lower limb/heel/ankle pain and patients (weight group of 40-60 kg) reported up to18%.

Patients in the age group of 51-80 years reported increase in pain (-8%) in the patients on CP. Patients in weight category of 61-90 kg and patients with lower back pain both CP and MP reported negative (-7%) percentage outcome in the patients on CP.

Trend analysis was performed for 4 key questions (reduction in pain, increase in pain, effect on daily activities, and effect on sleep interference) that were described every day by the patients during this study. Patients on CP showed improved reduction in pain over patients on MP, which was statistically significant (p=0.001) (see figure 9). CP cases reported less complaints regarding increase in pain from day 1 to 19, which was also statistically significant (p=0.004). There was no statistically significant difference for percentage effect on daily activities and sleep interference across both groups (see figure 9).

There were no serious or fatal adverse events during the course of the study. The adverse events were mostly of mild or moderate intensity. Around 15% of study patients reported adverse events. Most commonly reported adverse events were headache and hyperacidity. Proportion, type and intensity of adverse events were not significant across patients taking CP and MP. Overall, treatment with CP and MP was found to be safe in the population studied.

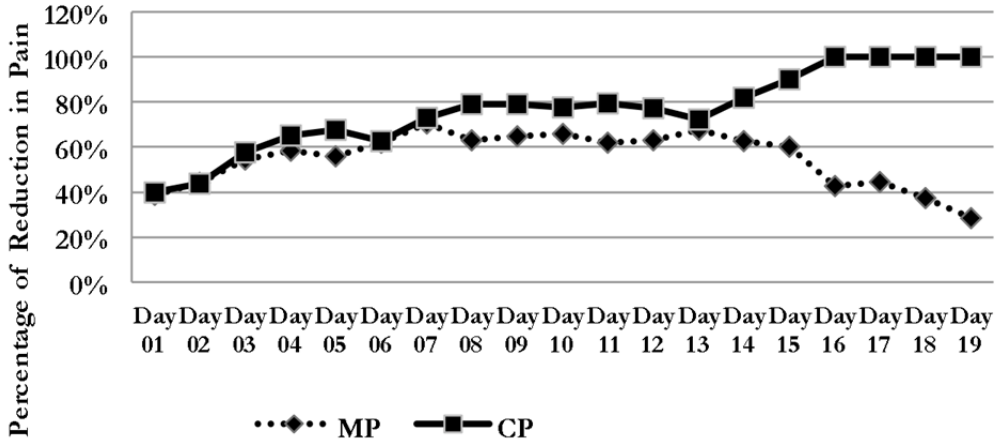

Figure 9. Percentage of reduction in pain based on patient diary (reduction in pain, increase in pain, effect on daily activities).

Discussion

In this observational research, we evaluated the effectiveness of highly diluted homeopathic preparations CP and MP as pain-relieving agents, based on the Law of Similars, which says that any substance having a capacity to produce certain symptoms also has a capacity to relieve the similar symptoms, if administered in ultra-diluted dose. Capsaicin alkaloids are known to produce pain in humans in crude form.

The major finding in this study suggests that CP and MP have effect as pain-relieving agents in highly diluted dose, supporting the basic homeopathic principle.

Most homeopathic medicines undergo Homeopathic Pathogenetic Trials (also called drug proving), an exploratory study to examine the effects on healthy human volunteers. In a separate unpublished research study of the Homeopathic Pathogenetic Trial, the author has established effect of ultra dilute dose of CP on healthy volunteers, through a randomized placebo controlled, double blind trial, where CP in 30c potency has produced significant symptoms pertaining to pain. Magnesium Phosphoricum (MP) is a tissue salt, which did not undergo such human trial (15). It has been in use as an analgesic based on clinical experience. It does not seem to be based on the Law of Similars. It may be noted that magnesium compounds have shown

efficacy in pain relief when administered in crude form (16, 17). Similarly, Capsaicin alkaloids have been used topically in pain relief (18).

The management of chronic pain is a huge challenge. This clinical trial has demonstrated significant relief in chronic painful conditions in a short span of two weeks, without producing adverse effects.

In this trial, efficacy of CP was found to be comparable with MP, one of the established homeopathic drugs. CP was found as effective as that of MP in reducing the intensity of pain, which was measured by NRS. All the volunteers were having various forms of chronic painful conditions, where some had persistent pain in spite of being on pain-relieving medicines. Total 27 (23.27%) patients were taking medication for pain management (pain-killers) at the baseline, and still having painfulness. Out of these 19 (70%) patients had shown up to 60% improvement in terms of reduction in pain after taking the investigational products; where 10 (37.04%) patients were on CP, while 9 (33.33%) on MP.

Lack of placebo arm in this comparative study could be considered a limitation. However, an attempt was made to compare the results of this study with that of placebo-controlled trials. For that purpose several systematic reviews and placebo-controlled trials evaluated the efficacy of oral treatments were studied. RG Gibson had conducted clinical trial "Homoeopathic therapy in rheumatoid arthritis: evaluation by double-blind clinical therapeutic trial", which had shown significant improvement in subjective pain, articular index, stiffness and in grip strength in those patients receiving homeopathy medicines whereas there was no significant change in patients who received placebo. The literature survey of clinical trials using homeopathy remedies have indicated comparable results in the past. (3,6)

This observational study showed greater effect of CP in subgroup of patients. This identified specific subgroup of patients can be studied to confirm these findings. Further research is needed to investigate the synergistic effect of both of these drugs (CP and MP) to effectively treat patients suffering from sub-acute and chronic pain.

More exploration based on the applied Law of Similars, using different substances having specific pathogenetic effects, may open doors to newer possibilities in the field of therapeutics.

Underlying mechanism leading to relief in symptoms by highly diluted substance having a capacity to produce similar symptom, needs to be investigated.

Conclusion

Ultra-molecular, highly diluted (potentized) Capsaicin alkaloids and Magnesium Phosphoricum were found effective and safe in reducing the intensity of pain, supporting the Law of Similars.

Acknowledgments

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