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Effectiveness of individualised homoeopathic medicines versus Calcarea Flourica 6x in the treatment of osteoarthritis: An open-label, randomised, pragmatic clinical trial

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Abstract
Background: Osteoarthritis is characterized by the destruction of joint cartilage. As the cartilage deteriorates, the bones of the joint begin to push against each other, causing pain and stiffness, often hindering or limiting movement. The joints which bear most of the weight of body is affected by osteoarthritis such as hip, knee, vertebra, and hand, it is a disease of cartilage in which interleukin play an important role.
Materials and methods: This prospective, open label, randomized controlled trial was conducted at Govt. Medical Homeopathic College, Bhopal, and Madhya Pradesh over a period of one year. A total of 60 patients with Osteoarthritis were randomized to receive Individualised Homoeopathic medicine (IH) or Calcarea Flourica 6X (CF) and outcome assessment was done using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) & Numerical Rating Scale (NRS) scales.
Result: Our study observed that WOMAC score at baseline, there was no significant difference in WOMAC score between IH and CF group (76.23±3.90 vs. 76.06±3.70; $p = 0.866$).
Conclusion: Both Individualized homeopathic treatment as well as Calcarea Fluor are effective in reducing pain and functional outcomes in patients with osteoarthritis. However, individualized homeopathic treatment provided a better efficacy than Calcarea Fluor.

Keywords: Osteoarthritis, Calcarea Flourica, individualised homoeopathic medicine, homoeopathy, WOMAC, NRS, pain

Introduction
The failure of the synovial joint that results from the interaction of several components, including genetic, metabolic, biochemical, and biomechanical, is the hallmark of osteoarthritis, which is a heterogeneous disease. Joint cartilage degeneration is a characterstic of O.A. The bones of the joint start to rub against one another as the cartilage deteriorates, producing discomfort and stiffness and frequently limiting or impeding movement. It is plausible to confidently diagnose OA as a clinical condition if any of the following circumstances apply: Age greater than 45, morning stiffness lasting less than 30 minutes or longer than an hour, enlargement of a bony joint, and restriction of range of motion are the four conditions that must be present. Among other soft tissue problems, rheumatoid arthritis, psoriatic arthritis, crystalline arthritis, hemochromatosis, bursitis, avascular necrosis, tendinitis, and radiculopathy, all are considered in the differential diagnosis [1, 2].

Epidemiology
The World Health Organization (WHO) estimates that 28% of people over 60 years worldwide have O.A., and that 80 % of those people have physical disabilities [3]. With 100 million individuals worldwide over the age of 45 years experiencing joint disability as a consequence of OA, which accounts for 15 % of all musculoskeletal disorders [4], OA is the most prevalent musculoskeletal disease in the world [5]. USA and Europe have the highest global representation [6]. Knee OA is the eighth most common cause of disability in men and the fourth most common in women worldwide [7]. According to the EULAR (European League against Rheumatism) committee report, 30 % of people over 65 have knee OA as seen on radiographs.

According to a study conducted, the age-standardized incidence rate (ASIR) of hip osteoarthritis increased globally between 1990 and 2019 from 17.02 per 100,000 people to 18.70 per 100,000 people [9]. A recent study in India found that the number of people with OA surged from 23.46 million in 1990 to 62.35 million in 2019. From 1990 to 2019, the number of DALYs attributable by OA rose from 0.79 million to 2.12 million. OA grew from the 23rd most frequent cause in 1990 to the 20th most frequent cause of YLDs in India in 2019, accounting for 1.48% of all YLDs. Knee OA was the most common form of OA, followed by hand OA [10]. Nearly 2% of people with OA over the age of 70 experience significant knee pain and disability, while around 80% of those with OA in India suffer knee discomfort, 20% of whom mention being unable to complete everyday activities and 11% requiring special care [11]. Approximately 40% of people have O.A. O.A. is the most common joint disease and the second most common rheumatologic condition in India, with prevalence estimates varying from 22% to 39% [12, 13].

The reduction of pain and functional loss are the main objectives of OA treatment. In the comprehensive treatment of the disease, both non-pharmacologic and pharmaceutical treatments are used. Individuals with mild symptoms can typically be treated with the former, whereas those with more severe disorders require a combination of both. [14–16} Optimal management includes non-drug and drug approaches that concentrate on preventing disease and stopping progression, rather than just focusing on palliation of disease. However, due to continuous adverse effects of long-term treatment with allopathic medicines, use of complementary therapies such as homeopathy etc., is on rise. Calcarea Flourica (CF) is one of the homoeopathic medicines for osteoarthritis, but research confirmation remains scarce. The drawbacks and negative effects of traditional medical treatment express concerns about osteoarthritis treatment being safe and efficient [17].A study found that there are no gastrointestinal toxicity or other side effects associated with homoeopathic treatment [18], and the few clinical trials that have been done to far favour homoeopathic treatment for individuals with osteoarthritis [19]. According to van Wassenhoven M, homoeopathy has a significant role in the management of arthritic conditions [20].

Homeopathy is a form of medicine that follows the "similia similibus curentur" principle (like cures like) [21]. The effectiveness of homoeopathy in general is well-known, and both the public and medical community have grown to trust it [18]. The use of homoeopathic medicine has also shown some promise in lowering oxidative stress [22]. The majority of the medicines used in homoeopathic treatment are highly potentized and dynamic [23]. Individualized homoeopathic care can enhance patients' quality of life and offer more alleviation [24]. Homoeopathy is the only branch of medicine that uses a constitutional approach to treatment. A constitutional remedy and a well-chosen, deep-acting homoeopathic remedy are equivalent. In one study, it was seen that homoeopathic remedies have a clear advantage in the treatment of osteoarthritis [25] and also a few low-potency homoeopathic treatment in the randomized controlled trials have showed that homoeopathy seemed to possess significant effects in OA [26]. A remedy with a unique nature and qualities is produced by the chemical union of lime and fluoric acid known as Calcarea Fluorica (CF) which is also known as Calcarea Fluoride. Common names include fluoride of lime, fluorspar. The inorganic compound CF, having the formula CaF2, is made up of the elements calcium and fluorine. It is an insoluble white solid. It occurs as the mineral fluorite. Dr. Schussler made use of this salt of calcium first. Allen's encyclopedia material medica volume X 398 [27]. The CF was first proved by Dr. J. B. Bell in 1874 [28]. CF is found in the surface of the bones and in the enamel of the teeth, especially, and it is one of the twelve remedies recommended by Schussler. In the bones it is useful for exostosis [29]. According to Dr. Boericke, dose mentioned as 3rd to 12th trituration [30]. Mishra and Jaiswal (2020) reported that the homoeopathic constitutional approach can be quite effective in treating O.A. and relieving pain [31].

Aim and Objectives

This study was aimed to evaluate the Effectiveness of Individualized Homoeopathic (IH) medicines versus Calcarea flour. 6X (CF) in the management of Osteoarthritis. Primary objectives of the study were to find out the efficacy of Individualized Homoeopathic (IH) medicine versus Calcarea flour. 6X (CF) in management of osteoarthritis, and to ascertain and shortlist the most frequently indicated homoeopathic medicines in the management of osteoarthritis. Secondary objective was to improve activity of daily living in osteoarthritis patients and decrease the suffering of patient.

Research question: Was there any significant difference between individualized homoeopathy (IH) and Calcarea Flourica 6X (CF) in the management of osteoarthritis.

Null hypothesis (H0): There was no difference between individualized homoeopathy (IH) and Calcarea Flourica 6X (C.F) in the management of osteoarthritis *i.e.*, both are equally effective.

Alternative hypothesis (H1): There was significant difference between individualized homoeopathy (IH) and Calcarea Flourica 6X (C.F) in the management of Osteoarthritis.

Materials and Methods

This prospective, open label randomized controlled trial was conducted with aim to compare evaluate the effectiveness of individualized homoeopathic (IH) medicines versus Calcarea Flour. 6x (CF) in the management of osteoarthritis at Govt. Medical Homeopathic College, Bhopal, Madhya Pradesh over a period of one year. In order to maintain an equal distribution between groups and a 1:1 ratio, a total of 60 patients with O.A. were randomized to receive individualized homoeopathic treatment or CF, *i.e.*, IH block of size 30 and CF: 30.Inclusion criteria were patients diagnosed with OA, age ≥ 35 years of either sex, any religion, provided their consent to participate in the study, with rheumatic and gouty diathesis with complaints of joints problems and newly diagnosed as OA, from various socio-economic status. Patients who met the following criteria were excluded from the study: those who were too ill for consultation, refused to give their consent, had diagnosed as unstable mental or psychiatric illness or other uncontrolled or life-threatening diseases that affected quality of life, or any gross pathology or organ failure, were pregnant or lactating, used drugs or alcohol excessively or depended on them, self-reported immune-compromised state, and were receiving homoeopathic treatment for any chronic disease

within last two months, severe OA requiring surgical intervention, non-ambulatory patients and patients age<35 years. In the IH group, final selection of the single individualized medicine was based on case taking in adherence with the standard homoeopathic guidelines, analysis, and evaluation of symptoms, framing symptom totality, Repertorisation, and final consultation with Homoeopathic Materia Medica. Individualized dose was selected on the judgment of susceptibility of the patients. Pain was measured using numerical rating scale (NRS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) index was used to measure functional outcome. In Numerical Rating Scale (NRS), patients were asked to circle the number between 0 and 10. Zero represented 'no pain at all' whereas the upper limit represented 'the worst pain ever possible. WOMAC Index was developed in 1982 at Western Ontario and McMaster Universities. Since its presentation by Bellamy *et al.* in 1988 [32], it has been validated in several countries. The test questions are graded from None (0), Mild (1), Moderate (2), Severe (3), and Extreme (4) on a scale of 0-4.With a possible score range of 0-20 for pain, 0-8 for stiffness, and 0-68 for physical function, the results for each subscale are added up. A typical WOMAC score is the result of adding the scores for each of the three subscales. The WOMAC score indicates the severity of the pain, stiffness, and functional limitations. Follow-up was done every 4 weeks up to 6 months. Data were recorded on case proforma, and entered Microsoft® Excel worksheet 2019, and exported into SPSS v21.0 (IBM, USA) for statistical analysis. Categorical variables were expressed as frequency, percentage, and compared using Chi square test with or without Yate's correction. Normality of data was determined using Shapiro-Wilk test. Normally distributed variables were compared between two groups using independent t-test. Comparison within a group at two time-intervals was made using paired t-test. P value<0.05 was considered statistically significant.

Results

Our study observed that there was no significant different in mean age of the patients between group IH and CF (54.00±11.71 years vs. 49.66±12.31 years; p = 0.168) (Table 1). Age-group based distribution also showed a non-significant difference in mean age between the groups (p = 0.186). Fifty-three percent patients in each group were males. Fifty-one percent of all the subjects belonged to rural areas. There was no significant different in mean BMI of the patients between group IH and CF (21.77±2.94 years vs. 21.67±3.07 years; p = 0.895). Thirty-three percent of all the subjects were overweight to obese. Sixty-six percent were married. Eighty percent of all the subjects had senior secondary level of education. Fifty percent of all the subjects were self-employed. Approximate 30% of the patients had income of < 10000 Rs per month. Our study observed that the patients in both groups were comparable in terms of distribution of age (p = 0.186), sex (p = 1.000), residence (P=0.438), BMI (p = 0.263), marital status (p = 0.416), education status (p = 0.290), employment status (p = 0.203), and income (p = 0.526). In comorbidities, 20% of IH and 33.33 of CF were diabetic, 26.67% of IH and 20% of CF were hypertensive, and 20% of IH and 26.67% of CF had other comorbidities including coronary artery disease, chronic obstructive pulmonary disease (COPD) etc. We found a non-significant difference in co-morbidities distribution between both groups (p = 0.462). In family history, 63.33% of IH and 40% of CF had no family history while 36.67% of IH and 60% of CF had family history of OA. We did not observe a non-significant difference in family history between both groups (p = 0.058). In previous joint injury, 60% 0f IH and 53.33% of CF had previous joint injury. There was no significant difference in distribution of previous joint injury between both groups (P=0.602). Medicine prescribed in IH group, five patients received Sulphur, three patients received Nux vomica, two patients each received Bryonia alba, Pulsatilla Nigricans, and Rhus toxicodendron, one patient each received Calcarea Carbonica, Causticum, Garphitis, Ignatia Amara, Lachesis, Lycopodium Clavatum, Medorrhinum, Mercurius Solubis, Natrum Muriaticum, Staphysagria and Veratrum Album.(Figure1) WOMAC score at baseline, there was no significant difference in WOMAC score between IH and CF group (76.23±3.90 vs. 76.06±3.70; p = 0.866). In IH compared to CF group at 2-month (65.60±4.03 vs. 70.23±2.99; p < 0.0001), 4-month (58.00±3.18 vs. 65.53±1.77; < 0.0001), and 6-month (55.06±1.52 vs. 56.63±1.69; p < 0.0001). We also observed a significant decrease in WOMAC score at 2-month, 4-month, and 6-month compared to baseline in both IH and CF group (p < 0.0001). NRS at baseline, there was no significant difference in NRS score between IH and CF group (6.46±1.56 vs. 6.20±1.12; p = 0.453). IH compared to CF group at 2-month (4.63±1.29 vs. 5.73±1.04; p = 0.001), 4-month (3.36±1.37 vs. 5.13±1.19 ;< 0.0001), and 6-month (2.20±1.32 vs. 4.63±1.27; p < 0.0001) (Table 2 & Figure 2). We also observed a significant decrease in NRS score at 2-month, 4-month, and 6-month compared to baseline in both IH and CF group (p < 0.0001) (Table 3 & Figure 3).

Table 1: Comparison of demographic characteristics of the study subjects (n=60)

Sr. No.	Variables	IH (N=30)	CF (N=30)	χ2 or T-Value	P Value
1	**Age (Years)**	54.00±11.71	49.66±12.31	1.369	0.168
2	**Age Group**				
	30-45	10 (33.33%)	13 (43.33%)	3.353	0.186
	46-60	10 (33.33%)	13 (43.33%)		
	>60	10 (33.33%)	4 (13.34%)		
3	**Gender**				
	Female	14 (46.67%)	14 (46.67%)	0.268	1.000
	Male	16 (53.33%)	16 (53.33%)		
4	**Residence**				
	Rural	17 (56.67%)	14 (46.67%)	0.6	0.438
	Urban	13 (43.33%)	16 (53.33%)		
5	Weight (Kg)	55.63±10.63	55.40±10.70	0.085	0.933

6	Height (cm)	159.26±6.25	159.36±6.42	0.061	0.952
7	BMI (Kg/m^2)	21.77±2.94	21.67±3.07	0.133	0.895
8	**BMI Group**				
	Underweight	6 (20%)	4 (13.33%)		0.263
	Normal	12 (40%)	18 (60%)	3.983	
	Obese	4 (13.33%)	5 (16.66%)		
	Overweight	8 (26.66%)	3 (10%)		
9	**Marital status**				
	Married	18 (60%)	21 (70%)	0.659	0.416
	Unmarried	12 (40%)	9 (30%)		
10	**Education Status**				
	Up to Class 10	6 (20%)	7 (23.33%)	2.47	0.29
	Up to Class 12	15 (50%)	19 (63, 34%)		
	Graduate and Higher	9 (30%)	4 (13.33%)		
11	**Employment Status**				
	Employed	8 (26.67%)	9 (30%)	3.181	0.203
	Unemployed	4 (13.33%)	9 (30%)		
	Self Employed	18 (60%)	12 (40%)		
12	**Income Status**				
	<10,000	10 (33.33%)	9 (30%)	1.281	0.526
	10,000-30,000	8 (26.67%)	12 (40%)		
	>30,000	12 (40%)	9 (30%)		

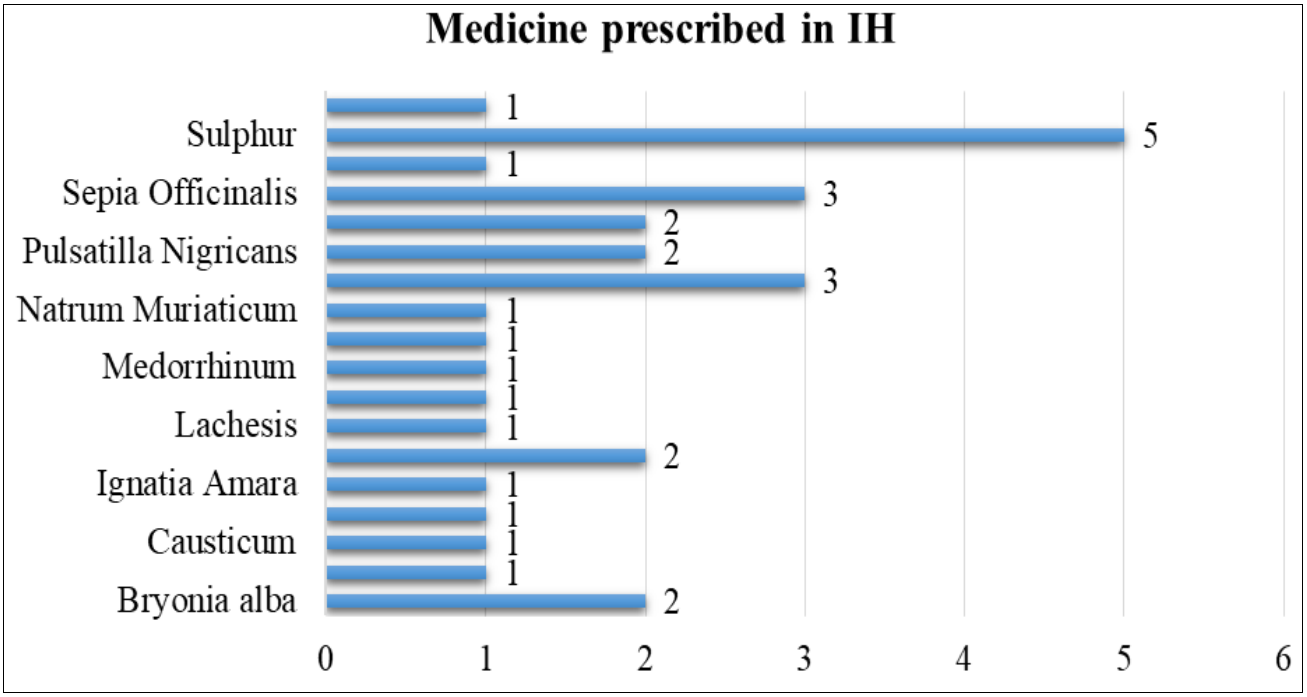

Fig 1: Medicines prescribed in Individualized Homoeopathic (IH) group

Table 2: Comparison of WOMAC score between IH and CF group

WOMAC	IH (n=30)	CF (n=30)	P value
Baseline	76.23±3.90	76.06±3.70	0.866
2 Month	65.60±4.03	70.23±2.99	<0.0001
4 Month	58.00±3.18	65.53±1.77	<0.0001
6 Month	55.06±1.52	56.63±1.69	<0.0001
P value	<0.0001	<0.0001	

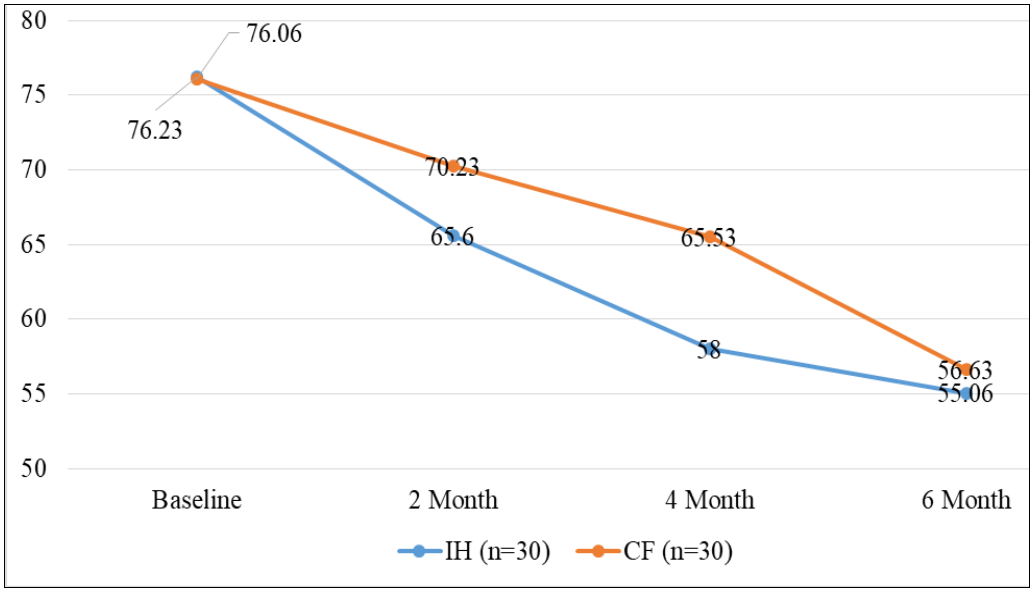

Fig 2: Line diagram showing trend in WOMAC score within the groups

Table 3: Comparison of NRS score between IH and CF group

NRS	IH (n=30)	CF (n=30)	P value
Baseline	6.46±1.56	6.20±1.12	0.453
2 Month	4.63±1.29	5.73±1.04	0.001
4 Month	3.36±1.37	5.13±1.19	<0.0001
6 Month	2.20±1.32	4.63±1.27	<0.0001
P value	<0.0001	<0.0001	

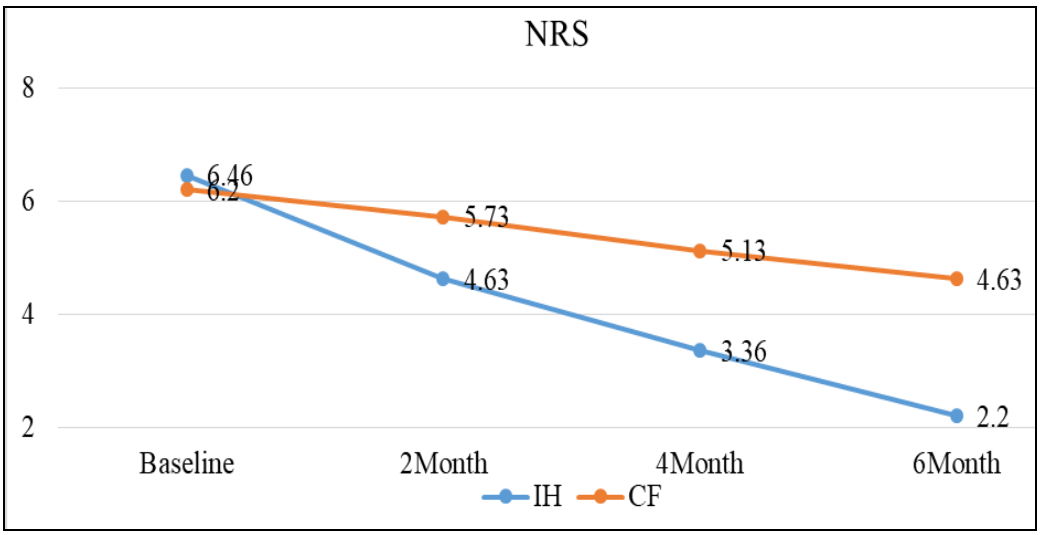

Fig 3: Line diagram showing trend in NRS score within the groups

Discussion

Principal Finding

There was no statistically significant difference in improvement of WOMAC and NRS scores between two groups that implied that both the constitutional homoeopathic medicines and Calcarea Fluor 6X were equally effective in the treatment of O.A over a period of 6months.

This prospective, open label randomized controlled trial was conducted with aim to compare evaluate the effectiveness of individualized homoeopathic (IH) medicines versus Calcarea Flour. 6x (CF) in the management of osteoarthritis at Govt. Medical Homeopathic College, Bhopal, Madhya Pradesh over a period of one year. A total of 60 patients with OA were randomized to receive individualized homeopathic medicine or CF. Findings of the study are discussed below.

Age

In our study, mean age of all the patients was 51.83 years. Approximate 57% of the patients aged above 45 years. Pal *et al.* reported that the prevalence of OA increases with increasing age. It was highest among the age group of 60 and above and lowest in people in the age group of 40–50 years [33]. According to a recent analysis by Krishnamurthy and Kumar, 35.3% of occurrences involved people between the ages of 70 and 80. According to the age group with the lowest prevalence of osteoarthritis in the age range of 40–49 years, a linear trend was seen, *i.e.*, 12.9%–35.3% in the age range of 70-80 years [34]. According to Desai *et al.*, 58% of

the OA patients were between the ages of 61 and 70 [35].

Gender

In our study, male and females were near equally affected by OA. A study performed by Srikanth *et al*., showed a definite increase in prevalence of OA cases was observed in women around the post-menopausal age group due to hormonal disturbance particularly estrogen playing a major role in it [36]. According to Davis *et al*., OA is more common in women over the age of 45 than it is in men under the same age bracket [37].

Residence

In our study, more than half of the patients belonged to rural areas. In comparison to towns (17.1%) and small cities (17.2%), Pal *et al*. found that the prevalence was higher in villages (31.1%) and big cities (33.1%) [33]. While Desai *et al*. reported that 64% of the patients belonged to urban background [35].

BMI

The development of OA is significantly influenced by BMI. In our study, 33.3% of the patients were overweight-obese. A recent cohort study by Martin *et al*. revealed a positive relationship between BMI and knee OA in women and suggested that people who are more active have a lower risk of developing knee OA [38]. In a meta-analysis done by Blagojević *et al*., it showed that BMI is a risk factor for OA [39]. According to Pal *et al*., increasing body mass index was observed to be associated with an increase in the prevalence of OA knees. Knee OA prevalence was substantially (P= 0.007) lower in persons who were underweight (28%), compared to participants who were normal weight and obese (33%). It was discovered that those who are overweight or obese have the highest prevalence [33].

Education status

In our study, approximately 80% of the patients had education level up to class 12. Desai *et al* reported that 65% of the patients with OA had class 10 level of education [35].

Employment status

In our study, 20% of the patients were unemployed. In a study by Pal *et al*., participants who were unemployed had the highest prevalence of knee OA. Despite being statistically significant (P = 0.0001), no cause-and-effect connection could be established. This is true since among the unemployed may be retired individuals. In these situations, the OA might have been brought on by ageing rather than unemployment. Participants who worked as daily wage employees or labourers had the lowest prevalence (22.2%) [33]. Desai *et al* reported that the prevalence of OA was highest among housewives followed by not working [35].

Co-morbidities

In this study, diabetes was the most common co-morbidity (27%) followed by hypertension (23%). People who have type 2 diabetes have an increased risk of osteoarthritis, likely due to obesity - a risk factor for type 2 diabetes - rather than to the diabetes itself. A recent report in adults ranging from 18–64 years showed that the prevalence of arthritis was 52% in those with T2DM compared to 27% in those without T2DM [40]. Schett *et al.* reported that type 2 diabetes predicts the development of severe OA independent of age and BMI [41].

WOMAC score

In this study, individualized homeopathic medicines were more effective in improvement in WOMAC score compared with CF at 2-months, 4-months, and 6-months. Although, WOMAC score improved in both the groups compared to baseline. 23 rheumatoid arthritis patients receiving orthodox first-line anti-inflammatory medication in addition to homoeopathy were compared to a similar group of 23 patients receiving orthodox first-line treatment in addition to an inert preparation in a study by Gobson *et al*. Subjective pain, articular index, stiffness, and grip strength significantly improved in patients getting homoeopathic treatments, but did not significantly change in those receiving placebos [42]. Rhus tox. 6X and fenoprofen were tested in a double-blind, placebo-controlled crossover research by Shipley *et al*. for osteoarthritis of the hip and knee. It was established that fenoprofen had advantageous analgesic and anti-inflammatory effects that were distinct from those of a placebo. The effects of Rhus tox 6X and the placebo were similar [43]. Individualized homoeopathic medicines provided in accordance with the law of similia improved the mean ADL from 35.85 to 19.08 in a study by Motiwalla *et al.* (p-0.0001). Mean pain decreased from 10.50 to 5.48 on the WOMAC Osteoarthritis Index survey form (p-0.0001) [44]. Mishra and Jaiswal reported that majority of the patients (73.3%) of this study group showed significant improvement in the clinical condition of Osteoarthritis with homeopathic medicines [31].

Pain score

In this study, individualized homeopathic medicines were more effective in improvement in pain compared with CF at 2-months, 4-months, and 6-months. Although, pain improved in both the groups compared to baseline. Motiwala *et al*., Mishra and Jaiswal *et al.* reported similar findings [44, 31].

Strengths, Limitations, Implication, and Recommendation of the Study

Main strengths of the Study

One of the study's main advantages was randomization, which meant that every participant had an equal chance of being assigned to one of the two arms. It served as "Gold standard" evidence of effectiveness. Equilibrium between groups, increased internal validity due to homogeneous study groups, reduced selection bias, unbiased allocation, generation of two comparable groups, balancing among potential confounders, facilitation of simple analysis, and the ability to clearly state that a difference was caused by the treatment were all benefits of randomization. The distribution of samples between the two arms was equitable thanks to the 1:1 randomization. Despite being modest, the sample size was nevertheless sufficiently powered to detect changes in the specified outcome measure but underpowered to be generalizable; hence, cautious interpretation was necessary. The two trial arms had no significant difference between them at baseline ensuring comparability. Prospective study design allowed causal inference to be drawn. No placebo control was used; hence, ethically the study was less vulnerable. Second strength is use of WOMAC score which measures physical function,

pain, and stiffness, and NRS for pain. WOMAC score is the one of the best indicators for improvement in knee functions of O.A.

Weakness of the study

Because it was the first study of its kind in homoeopathy, the study's approach was exploratory. Instead of using effect size, assumptions were used to calculate sample size. There was no use of blinding during the open trial. Because there was no prior study with a similar design, patient selection bias, treatment assignment bias, patient evaluation bias, and data analysis bias may have had an impact on the study's conclusion. The experiment also suffered from the lack of any outcome measures specific to homoeopathy or diseases (such as the Glasgow Homeopathic Hospital Outcome Scale). The 6-month follow-up period was too brief, particularly when dealing with chronic conditions. In the study design, we kept provision for only pair-wise comparisons; rather comparisons using repeated measures would have been a better analysis plan than this.

Unanswered questions and future research

Whether Calcarea Fluor 6X can produce any treatment effect beyond placebo has not still been evaluated; should be experimented using Double Blind Randomized Placebo Control Trial design. Besides, pragmatic non-inferiority trials having standard therapy in control arm need to be conducted evaluating effectiveness of Calcarea Fluor 6X in prescription.

Conclusion

Both individualized homeopathic treatment as well as Calcarea Fluor. Are effective in reducing pain and functional outcomes in the patients with osteoarthritis of knee; however, individualized homeopathic treatment provided a better efficacy than Calcarea Fluor. So, on the basis of statistical analysis and the value of probability derived from such analysis, null hypothesis of no difference was accepted and the alternative hypothesis of probable difference was rejected and further trials of similar design and enhanced methodological rigor are warranted.

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Conflict of Interest

Not available

Financial Support

Not available

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