Journal of Advanced Zoology
ISSN: 0253-7214
Volume 45 Issue 01 Year 2024 Page 1021:1029

Evaluation Of Novel Iontophoretic Gel Containing Symphytum Officinale On Knee Osteoarthritic Patients

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Abstract

Introduction: One of the most prevalent disorders causing pain in the musculoskeletal system and eventual disability is osteoarthritis (OA). The concurrent use of pharmaceutical and non-pharmacological therapies is an essential component of the therapy. The purpose of this study was to assess the efficacy of iontophoresis therapy in patients with osteoarthritis (OA) of the knee joints using a newly formulated Gel containing symphytum officinale.
Material and Methods: The study included 126 patients with Knee osteoarthritis treated at the Outpatient department at Delhi Pharmaceutical Sciences & Research University, New Delhi. Three groups were randomly selected: group I (n = 42), received iontophoresis with newly developed Gel containing symphytum officinale treatment was applied followed by exercise protocol, group II (n = 42) received iontophoresis with Indomethacin gel was applied followed by exercise protocol , and group III (n = 42) received placebo treatment with knee exercise protocol only. The Visual analog scale (VAS), Western Ontario and McMaster Universities Arthritis Index (WOMAC), Pittsburg sleep quality index (PSQI) & Walking cadence were used for the clinical evaluation of the patients.
Results: Patients treated with a new gel containing symphytum officinale showed significant improvement in all assessed parameters compared to those treated with Indomethacin gel and placebo.
Conclusions: The most favorable iontophoresis resulted from the introduction of a new gel containing symphytum officinale, followed by an exercise protocol.

Keywords: knee osteoarthritis; iontophoresis with gel containing symphytum officinale.

INTRODUCTION:

Osteoarthritis (OA) is the most prevalent musculoskeletal disease, causing impairments in everyday functioning, particularly in older adults. According to WHO, in developed countries, it is one of the most prevalent causes of disability.[1] OA affects joints, with knee joints being most affected. Pathological lesions occur due to imbalance between repair and damage processes in cartilage tissue. With long-term effects including physical impairment and disability, the condition affects the whole joint and causes symptoms including pain, stiffness, and muscular weakness. It is characterized by increasing, individual variability.[2] OA therapeutic techniques involve combining pharmaceutical and non-pharmacological therapies to manage pain, enhance joint functionality, and initiate cartilage regeneration. Patient involvement in therapy planning, education, equipment supply, and rehabilitation is crucial, with physiotherapeutic intervention used early. A key component of treatment is physical therapy, which reduces increased muscular tension and edema in addition to reducing pain. Consequently, this improves overall health by enhancing the joint's range of motion.[3] Variables like age, sex, degenerative progression, and concurrent disorders influence the choice of techniques and therapy for OA. To improve patient quality of life and delay surgery, treatment approaches should be customized to the patient's needs and physical condition. Common physical techniques used in OA treatment include iontophoresis and galvanic therapy, which use direct current.[4]

Iontophoresis is a treatment that uses electrolytic dissociation of chemical compounds to introduce medicinal ions into deeper tissues, providing strong analgesic, anti-inflammatory, and anti-swelling effects. Iontophoresis is a technique that allows for high medication concentration without oral delivery by allowing a substance's ions to enter the skin through sweat glands. This technique achieves a high concentration in the target tissue, lowering the possibility of overdosage and adverse consequences. There are several factors that impact the efficacy of iontophoresis therapy. These consist of the compound's physicochemical characteristics, such as its charge and size of particles, concentration, and/or the presence of additional ions in the preparation. Important factors to consider are the type of electrodes used, the duration of the treatment, the strength and type of current flow, and the equipment employed. The biological variables that affect the therapy's effectiveness include the temperature and surface area of the skin as well as local blood flow.[5]
In this study, 126 patients with osteoarthritis of the knee joints underwent iontophoresis with newly developed gel containing symphytum officinale & indomethacin gel, followed by an exercise protocol. The patients' pain, physical function, sleep quality, and gait patterns were all evaluated. The literature does not contain any studies comparing the effects of indomethacin gel and iontophoresis with gel containing Symphytum officinale on walking speed, pain, function, or sleep quality in individuals with osteoarthritis of the knee. The use of a newly formulated gel containing Symphytum officinale in conjunction with an exercise regimen yielded the most beneficial results from iontophoresis. Comfrey extract, derived from Symphytum officinale L., has anti-inflammatory, antibacterial, antifungal, and anti-inflammatory properties. It also exhibits antioxidant properties and benefits human skin fibroblasts. Comfrey contains allantoin, which stimulates cell division, promotes tissue formation, aids wound healing, and promotes tissue regeneration. It also enhances local metabolism by reducing neuromuscular excitability and increasing vascular flow, thereby promoting tissue regeneration and improving local metabolism. Direct current iontophoresis reduces muscular tension, enhancing pain reduction. Symphytum officinale gel is a safe and effective substitute for NSAIDs due to its unique properties.[5]

Methodology

The study involved 126 patients with knee osteoarthritis at Delhi Pharmaceutical Sciences & Research University's outpatient department. The severity of the lesions was assessed using the Kellgren–Lawrence scale. The patients had a mean age of 56.16 years, with 56.58% having 2nd degree degenerative lesions and 27.27% having 1st degree degenerative lesions. The majority had problems with their right knee, 29 with their left knee, and 70 with both knee joints. On average, the duration during which that pain persisted was 55.78 months or around 4.5 years. The participants in the study were allocated into three groups by random. Group I (n = 42), received iontophoresis with newly developed Gel containing symphytum officinale treatment was applied followed by exercise protocol , group II (n = 42) received iontophoresis with Indomethacin gel was applied followed by exercise protocol , and group III (n = 42) received placebo treatment with knee exercise protocol only for 3 months (4 days a week, total 18 sessions) followed by 1 month follow up program. The electrical muscle stimulator was used to carry out the therapy. The therapy, initially 15 minutes long, was repeated daily for 20 minutes, with the dosage adjusted based on the patient's perception. The intensity was maintained at 0.2 mA/cm2 to 2 mA/cm2. Patients provided informed consent and underwent a clinical

assessment before and after the therapy's start. The conducted research was approved by the Biomedical Research Human Ethics Committee (DPSRU-BREC), DPSRU & Institutional Animal Ethics Committee, DPSRU has been taken. This study has been registered in clinical trial registry and got trial acknowledgement number (CTRI/2022/06/043155).

Clinical Evaluation

The study involved patients undergoing a physical examination and interview, using scales and questionnaires to assess pain severity.
The Visual Analogue Scale (VAS) was used to measure pain severity, with 0 indicating no discomfort and 10 indicating excruciating pain.
The McMaster University and Western Ontario Arthritis Index was used for physical function evaluation, with five questions focusing on pain, two on stiffness, and seventeen on daily life task difficulty. Quality of sleep assessment on
The Pittsburgh Sleep Quality Index (PSQI) : It is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval. Walking cadence assessment on Cadence: It is a rate representing quantified steps displayed over time.

Statistical Analysis

The method of descriptive statistics has been used to describe the demographic and clinical characteristics of the participant and the method of inferential statistics has been used to determine the efficacy of various interventions in treatment of knee osteoarthritis. The normality was analyzed using Kolmogorov Smirnov test. The data distribution of the sample included in the study was assessed as normal. Kruskal wallis test was used to analyze the between group effect by comparing scores of pre-intervention (at baseline), post-intervention and follow-up scores of VAS in all the three groups. Table 5.4 shows the result of between group comparisons and Table 5.5 shows within group comparisons of the outcomevariable using Wilcoxon signed rank test. The between group comparison for the outcome variable WOMAC, walking speed & quality of sleep was analyzed using one way ANOVA & Within group comparison for the outcome variable WOMAC, walking speed & quality of speed was analyzed using repeated measure ANOVA. Post hoc multiple comparisons was done using Mann Whitney U test for the significant variables. T test was used to measure pre-post and follow up differences within individual groups of WOMAC, walking speed & quality of sleep.

Results:

i)VAS

Kruskal wallis test was used to analyze the between group effect by comparing scores of pre-intervention (at baseline), post-intervention and follow-up scores of VAS in all the three groups. Table 1.1 shows the result of between group comparisons and Table 1.2 shows within group comparisons of the outcome variable using Wilcoxon signed rank test. Table 1.1 shows the between group comparisons of the outcome variables at various time points of assessment. The result of between group comparisons using Kruskal wallis test showed statistically significant between group differences in pain (VAS) in all the three groups post intervention and at follow up. At the baseline, there were no statistically significant between group differences in the pain. Post treatment, there was a statistically significant difference in pain ($\chi2$= 10.058, p=0.007*) when between group comparisons were done. The statistically significant difference in pain was also seen at follow up ($\chi2$= 12.709, p= 0.002*). Since a statistically significant difference existed in VAS among the three groups, post hoc multiple comparisons was done using Mann Whitney U test for the significant variables.

Table 1.1: Between groups Comparison of Pre-Intervention, Post -Intervention and Follow-Up of VAS

		N	Mean	Standard Deviation	Median	Kruskal Wallis ($\chi2$)	p-value
Pre	Group-A	42	7.79	.75	8.00	3.305	.121
	Group-B	42	7.76	.76	8.00		
	Group-C	42	7.50	.83	8.00		
Post	Group-A	42	5.50	.74	6.00	10.058	.007**
	Group-B	42	5.69	.78	6.00		

	Group-C	42	5.95	.66	6.00		
Follow-up	Group-A	42	5.64	.76	6.00	12.709	.002**
	Group-B	42	5.79	.75	6.00		
	Group-C	42	6.29	1.02	6.00		

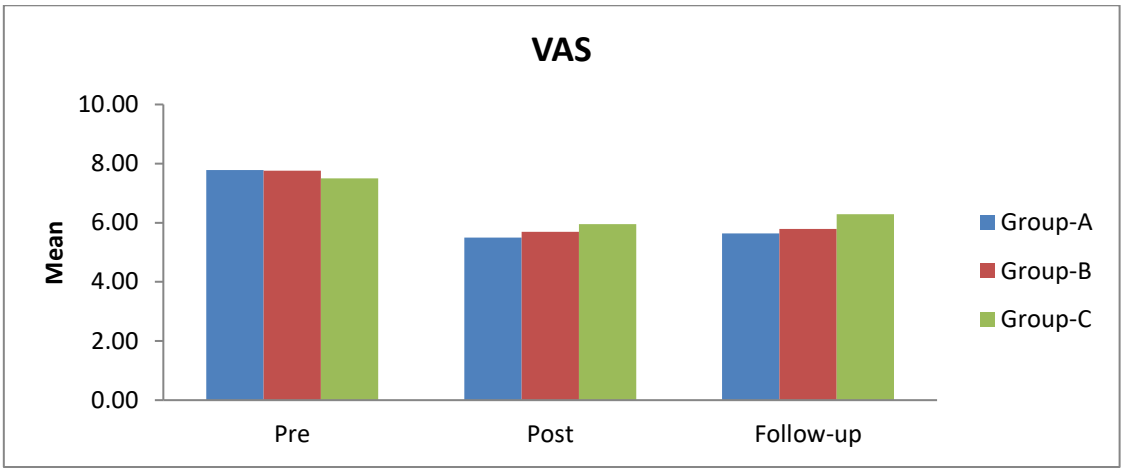

Figure 1.1: Graph Represents the mean Pre- Intervention, Post- Intervention and Follow-Up Scores of VAS

Table 1.2: Within Group Comparison of Pre-Intervention, Post -Intervention and Follow-Up of VAS

		N	Mean	Standard Deviation	Median	Wilcoxon Signed Ranks (z)	p-value
Group-A	VAS-Pre	42	7.79	.75	8.00	ref	
	Post	42	5.50	.74	6.00	6.481	.0001**
	After 1 month	42	5.64	.76	6.00	6.285	.0001**
Group-B	VAS-Pre	42	7.76	.76	8.00	ref	
	Post	42	5.69	.78	6.00	6.481	.0001**
	After 1 month	42	5.79	.75	6.00	6.481	.0001**
Group-C	VAS-Pre	42	7.50	.83	8.00	ref	
	Post	42	5.95	.66	6.00	6.285	.0001**
	After 1 month	42	6.29	1.02	6.00	5.596	.0001**

ii) WOMAC:

The between group comparison for the outcome variable WOMAC was analyzed using one way ANOVA. Analysis of variance was used to analyze the with-in group effect by comparing the median scores of pre-intervention (at baseline), post-intervention and follow-up scores of WOMAC in all the three groups. The results of the test showed astatistically significant difference among post-intervention, and follow-up scores of WOMAC with p value <0.05. The between group comparison for the outcome variable WOMAC was analyzed using one way ANOVA. The between group comparisons for WOMAC showed there was no statistically significant between group differences pre-treatment (F=1.603, p= 0.205), while significant differences were found in the groups post treatment (F=6.944, p=0.001) and at follow up (F=8.540, p= 0.0001). Analysis of variance (ANOVA) was used to analyze the with-in group effect by comparing the median scores of pre-intervention (at baseline), post-intervention and follow-up scores of WOMAC in all the three groups. The results of the test showed a statistically significant difference with F value = 246.748, p=0.0001.

Table 1.3: Between groups Comparison of Pre-Intervention, Post -Intervention and Follow-Up of WOMAC

		N	Mean	Standard Deviation	Median	F-value	p-value
Pre	Group-A	42	68.21	11.02	69.00	1.603	.205
	Group-B	42	68.17	10.96	69.00		
	Group-C	42	71.64	8.40	73.00		
Post	Group-A	42	60.38	10.76	62.50	6.944	.001**
	Group-B	42	61.93	11.30	64.00		

	Group-C	42	68.33	8.89	70.00		
Follow-up	Group-A	42	60.45	11.19	63.00	8.540	.0001**
	Group-B	42	61.55	11.28	64.00		
	Group-C	42	69.12	8.73	70.00		

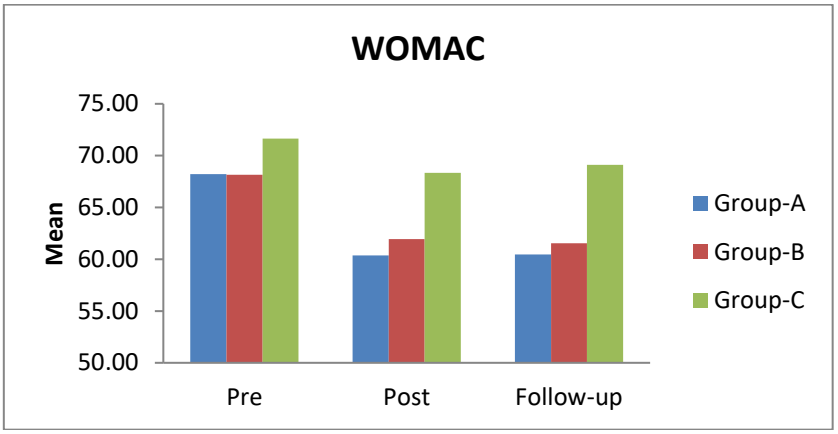

Figure 1.2: Graph Represents the Mean of Pre-Intervention, Post-Interventionand Follow-Up Scores of WOMAC for the three groups

Table 1.4: Multiple Comparisons among the Post-Intervention and Follow-Up Scores of WOMAC

Dependent Variable			Mean Difference (I-J)	Std. Error	p-value
Post	Group-A	Group-B	-1.54762	2.263	.792
		Group-C	-7.95238*	2.263	.003**
	Group-B	Group-A	1.54762	2.263	.792
		Group-C	-6.40476*	2.263	.021*
	Group-C	Group-A	7.95238*	2.263	.003**
		Group-B	6.40476*	2.263	.021*
Follow-up	Group-A	Group-B	-1.09524	2.284	.891
		Group-C	-8.66667*	2.284	.001**
	Group-B	Group-A	1.09524	2.284	.891
		Group-C	-7.57143*	2.284	.005**
	Group-C	Group-A	8.66667*	2.284	.001**
		Group-B	7.57143*	2.284	.005**

iii) Cadence

The between group comparison for the outcome variable waking speed was analyzed using one way ANOVA. Analysis of variance was used to analyze the with-in group effect by comparing the median scores of pre-intervention (at baseline), post-intervention and follow-up scores of waking speed in all the three groups. The results of the test showed astatistically significant difference among post-intervention, and follow-up scores of waking pattern with p value <0.05. The between group comparisons for walking speed showed there was no statistically significant between group differences pre-treatment (F=0.410, p= 0.665), while significant differences were found in the groups post treatment (F=3.425, p=0.036) and at follow up (F=4.629, p= 0.012). Analysis of variance (ANOVA) was used to analyze the with-in group effect by comparing the median scores of pre-intervention (at baseline), post-intervention and follow-up scores of walking speed in all the three groups. The results of the test showed a statistically significant difference with F value = 191.922, p=0.0001

Table 1.5: Between groups Comparison of Pre-Intervention, Post -Intervention and Follow-Up of Walking speed

		N	Mean	Standard Deviation	Median	F-value	p-value
Pre	Group-A	42	114.36	9.88	114.00	.410	.665
	Group-B	42	114.36	9.88	114.00		
	Group-C	42	115.93	7.59	116.00		
Post	Group-A	42	123.81	8.75	124.00	3.425	.036*
	Group-B	42	122.67	9.59	123.00		
	Group-C	42	119.10	7.34	121.00		
Follow-up	Group-A	42	123.07	9.58	123.50	4.629	.012*
	Group-B	42	123.17	8.99	123.50		
	Group-C	42	118.12	7.37	120.50		

Table 1.6: Pairwise Comparisons walking pattern

Walking Pattern		Mean Difference (I-J)	Std. Error	p-value
Pre	Post	-6.976*	.474	.0001**
	Follow-up	-6.571*	.477	.0001**
Post	Pre	6.976*	.474	.0001**
	Follow-up	.405	.167	.051
Follow-up	Pre	6.571*	.477	.0001**
	Post	-.405	.167	.051

iv) Pittsburgh Sleep Quality Index:

The between group comparison for the outcome variable quality of sleep was analyzed using one way ANOVA. Analysis of variance was used to analyze the with-in group effect by comparing the median scores of pre-intervention (at baseline), post-intervention and follow-up scores of quality of sleep in all the three groups. The results of the test showed a statistically significant difference among post-intervention, and follow-up scores of quality of sleep with p value <0.05. The between group comparison for the outcome variable quality of sleep was analyzed using one way ANOVA. The between group comparisons for walking pattern showed there was no statistically significant between group differences pre-treatment (F=0.035, p= 0.966), while significant differences were found in the groups post treatment (F=3.742, p=0.026) and at follow up (F=3.426, p= 0.036). Analysis of variance (ANOVA) was used to analyze the with-in group effect by comparing the median scores of pre-intervention (at baseline), post-intervention and follow-up scores of walking pattern in all the three groups. The results of the test showed a statistically significant difference with F value = 326.341 p=0.0001.

Table 1.7: Between groups Comparison of Pre-Intervention, Post -Intervention and Follow-Up of quality of sleep

		N	Mean	Standard Deviation	Median	F-value	p-value
Pre	Group-A	42	6.88	2.57	7.00	.035	.966
	Group-B	42	6.88	2.57	7.00		
	Group-C	42	6.76	1.97	7.00		
Post	Group-A	42	5.21	1.99	5.00	3.742	.026*
	Group-B	42	5.00	2.13	5.00		
	Group-C	42	4.17	1.34	4.00		
Follow-up	Group-A	42	5.14	2.07	5.00	3.426	.036*
	Group-B	42	5.81	2.32	5.00		
	Group-C	42	4.67	1.57	5.00		

Table1.8: Pairwise Comparisons quality of sleep

Quality of sleep		Mean Difference (I-J)	Std. Error	p-value
Pre	Post	2.048*	.094	.0001**
	Follow-up	1.635*	.098	.0001**
Post	Pre	-2.048*	.094	.0001**
	Follow-up	-.413*	.057	.0001**
Follow-up	Pre	-1.635*	.098	.0001**
	Post	.413*	.057	.0001**

Discussion:

The current guidelines for conservative non-surgical treatment of osteoarthritis emphasize the use of both pharmaceutical and non-pharmacological therapies. The focus is on non-pharmacological approaches to ensure safety and efficacy, as pharmaceutical treatment has numerous drawbacks and adverse effects.[6]

This present study tested the efficacy of iontophoresis using a new gel containing symphytum officinale and indomethacin gel, followed by an exercise protocol, in 126 knee joint osteoarthritis patients. Three groups were randomly selected: group I (n = 42), received iontophoresis with newly developed Gel containing symphytum officinale treatment was applied followed by exercise protocol , group II (n = 42) received iontophoresis with Indomethacin gel was applied followed by exercise protocol , and group III (n = 42) received placebo treatment with knee exercise protocol only. The Visual analog scale (VAS), Western Ontario and McMaster Universities Arthritis Index (WOMAC), Pittsburg sleep quality index (PSQI) & Walking cadence were used for the clinical evaluation of the patients.

No studies evaluating the effects of indomethacin gel and iontophoresis with gel containing Symphytum officinale on pain, function, sleep quality, and walking habits in people with osteoarthritis have been found in the literature. When iontophoresis with a newly produced gel containing Symphytum officinale was used when combined with an exercise regimen, the most positive effects were observed. Recent studies show that iontophoresis, a non-invasive treatment method, improves vascular flow and reduces neuromuscular excitability by delivering therapeutic ions into tissues. This method is particularly advantageous for osteoarthritis treatment as it allows medication to be applied directly to the affected tissue, avoiding internal organs and adverse effects. This treatment is considered an option for treating osteoarthritis.[7]

To our knowledge, no study has been reported till now regarding to evaluate the effectiveness of iontophoresis with gel containing symphytum officinale alongwith comparative evaluation with indomethacin gel on pain, function, quality of sleep and walking patterns in knee OA patients. The most favorable effect of iontophoresis was observed in the case of iontophoresis with newly developed Gel containing symphytum officinale introduced followed by exercise protocol. Studies have shown that iontophoresis can be combined with NSAIDs and steroid medications to treat OA patients. The appropriate polarization for ketoprofen injection into the rat knee joint was determined. NSAIDs have shown improvements in walking speed, pain, and active range of motion after iontophoresis with 5% Ibuprofen, as well as a significant reduction in pain and increased functional ability and knee extensor muscle strength after iontophoresis with Piroxicam gel.[8]

A study on an osteoarthritic rat model found that iontophoretic administration of ketoprofen choline chloride significantly reduced knee inflammation and discomfort. This suggests that comfrey, a plant with antibacterial, antifungal, and anti-inflammatory properties, can be used to enhance its analgesic effects.[9] Comfrey root inhibits the formation of a pro-inflammatory environment in human endothelial cells, reducing the expression of pro-inflammatory markers like E-selectin, VCAM1, ICAM1, and COX-2 when exposed to IL-1. This effect is particularly noticeable in the extract's mucilage-depleted fraction. Comfrey suppresses NF-kB signaling at two stages: preventing NF-kB p65 nucleo-cytoplasmatic shuttling and transactivation, and activating IKK1/2 and IkBa degradation. Symphytum officinale gel, despite its limited localized inflammatory features, exhibits significant anti-inflammatory properties, with Sarasapogenin, a component, enhancing its anti-inflammatory effect.[10] Vostinaru et al. (2019) stated that the study evaluated the antinociceptive and anti-inflammatory properties of a root extract of S. officinale. The extract showed a strong peripheral antinociceptive effect in rats, raising threshold pain by 58%. It also inhibited acetic acid-induced abdominal constrictions in mice. A glycopeptide from the extract also showed dose-dependent antichloristic action on rat paw edema caused by carrageenan, preventing prostaglandins and leukotriene production. In fact, it has been reported that the

majority of S. officinale's anti-inflammatory properties are due to the presence of polyphenols that selectively inhibit COX-2 and triterpenes that inhibit various stages of inflammation, including histamine release, cyclooxygenase (COX) and lipoxygenase (LOX) activity, and nitric oxide production.[11]
Symphytum officinale, a plant with local anesthetic properties, activates endogenous opioid-dependent analgesic pathways through iontophoresis with direct current, enhancing joint function and motion. This technique also improves epidermal blood flow, enhancing local metabolism and blood supply. Symphytum officinale's components also enhance peripheral circulation, microcirculation, tissue metabolism, and oxygenation, eliminating toxic products and promoting tissue oxygenation.[12] Symphytum officinale, a plant rich in plant-based compounds like allantoin, madecassic acid, and sarasapogenin, has numerous benefits including reducing muscle tenseness, accelerating healing processes, and calming stress due to its limbic system influence. These compounds have analgesic and anti-inflammatory properties, limiting the formation of prostaglandin and nitric oxide, which have antioxidant effects. A study found that physical therapy using symphytum officinale gel resulted in superior results than indomethacin gel, reducing discomfort and promoting overall health.[13]
All patient groups exhibited improved physical activity, decreased pain intensity and frequency, and less frequent use of medicines, according to the WOMAC questionnaire; however, iontophoresis had a more positive result. All patient groups in this research had improvements in their functional status and decreased pain severity. Compared to indomethacin gel, iontophoresis using gel containing symphytum officinale had a statistically significant superior result. Prior research on the use of NSAIDs and steroid medications with iontophoresis for the treatment of OA patients. A study aimed to determine the appropriate polarization for ketoprofen injection into the rat knee joint. Studies show improvements in walking speed, pain, and active range of motion after iontophoresis with 5% Ibuprofen. Iontophoresis with Piroxicam gel reduces pain, increases functional ability, and strengthens knee extensor muscles. In an osteoarthritic rat model, iontophoretic administration of cationic ketoprofen choline chloride significantly reduces knee inflammation and discomfort.[14] Dexamethasone iontophoresis was found to support a more notable clinical and functional improvement in the treatment of patients with knee osteoarthritis. Although there were no significant differences between group I (n = 42), received iontophoresis with newly developed Gel containing symphytum officinale treatment was applied followed by exercise protocol , group II (n = 42) received iontophoresis with Indomethacin gel was applied followed by exercise protocol, due to short duration study small sample size. The knee joint is crucial for maintaining good posture and mobility, so thorough treatment is essential to prevent functional changes in nearby joints, like the foot, potentially impacted by OA.[15]

Conclusions:

1. In the group of patients who underwent iontophoresis with gel containing symphytum officinale followed by exercises, statistically significant improvements in the degree of pain intensity, functional capacity, walking speed & quality of sleep was demonstrated in relation to the patients who underwent the iontophoresis with Indomethacin followed by exercises & placebo effect followed by exercises
2. Taking into account the above results, it is worth considering the use of iontophoresis with gel containing symphytum officinale in patients with osteoarthritis of the knee joint.

Future Scope of the Study:

1. Further studies can be done for longer period of evaluation with increased number of sessions & large sample size.
2. Further studies can be done on histological analysis for cartilage growth.

Conflict of Interests: NIL

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