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Symptoms-modifying effects of electromotive administration of glucosamine sulphate among patients with knee osteoarthritis

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Background: Most trials on symptom-modifying effects of glucosamine are limited to administration through oral route with dearth of empirical data on the use of electromotive force.
Objective: The study determined the effects of glucosamine sulphate (GS) iontophoresis (IoT) on radiographic parameters of patients with knee osteoarthritis (OA).
Methods: Fifty-three patients were randomly assigned to three groups. About 1 g each of GS was administered using IoT and cross-friction massage (CFM) for participants in groups 1 (IoT) and 2 (CFM), respectively. Group 3 ((Combined therapy) CoT) received 1 g of GS using both IoT and CFM. Interventions were twice a week for 12 weeks. Analysis of variance (ANOVA) was used to analyze the data ($p < 0.05$).
Results: After 12 weeks, the medial joint space width (JSW) of the CFM group was significantly higher than that of IoT and CoT groups ($p = 0.005$ and $p = 0.004$). Lateral JSW of IoT group was significantly higher than both CFM ($p = 0.001$) and CoT groups ($p = 0.01$). There were significant decreases in pain intensities;

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increase in knee flexion and physical functions across the groups ($F = 9.33, p = 0.01; F = 3.23, p = 0.01; H = 4.97, p = 0.01$, respectively).

Conclusion: It was concluded that there were significant decreases in the degenerative changes at the knee joint.

Keywords: Osteoarthritis; glucosamine; electromotive administration; degenerative changes.

Introduction

Osteoarthritis (OA) is the most common arthritis with about 3.8% affecting the knee and hip joints.[1] Approximately 10% and 18% of men and women, respectively, present with multifarious symptoms and radiological evidence in more than 50% of people over 65 years of age.[2,3] There is an increasing prevalence of OA with resultant decrease in functional capacities of patients.[4] The earliest signs of knee OA are narrowing of the medial compartment of the joint, sub-chondral sclerosis, cystic changes in the articular surfaces, and spur formation on the tibia spine.[5] The measurement of the distance between the distal femur and the proximal tibia is the joint space width (JSW) and it is an indirect way of measuring cartilage thickness. The JSW is reproducible for the assessment of progressive knee cartilage degenerations, and evaluation of disease-modifying effects of therapies.[6,7] The diagnosis of OA is based on the combination of typical mechanical pain symptoms and physical findings in the joints. OA has traditionally been diagnosed with radiographs that demonstrate JSW and osteophytes.[8]

The main goal of managing OA includes alleviation of pain and improving functional abilities and main drugs of choice are non-steroidal anti-inflammatory drugs (NSAIDs), but the oral and injectables are not without potential hazards. The adverse effects include gastrointestinal disorders and reduction in body immunity, particularly in the elderly.[9] In view of this, there is an increasing quest in medical technology towards establishing safer and effective means of delivering medications beside these common methods. Hence, drug administration using electromotive forces (iontophoresis (IoT) and phonophoresis) are being considered as alternatives in clinical physiotherapy practice. Although, pharmacokinetic parameters of most of these drugs have not been analytically established after administration through the use of electromotive forces, the successes attached to

the findings are clinical indications in which the medications are delivered in sufficient amount to the targeted tissues.[4,10,11] In IoT, there is percutaneous absorption through three main pathways: the intercellular (paracellular) pathway between the conneocytes along the lamellar lipids, the intracellular (transcellular) pathway through the cells or the appendageal (shunt) pathway via hair follicles, sweat ducts and secretary glands.[12] Patients with OA should receive a combination of non-pharmacologic and pharmacologic treatment.[13] Amongst drugs which have been speculated to be disease-modifying are glucosamine and chondroitin, but the magnitude of their effects remains unclear and controversial. The effectiveness of administration of glucosamine on slowing progression of OA is still shrewd with speculation.[14] The evidence that it can modify the structure of joints is still early and inconclusive. Some clinical trials have shown that glucosamine may prevent or slow down the loss of cartilage rather than re-growing it.[15,16] Speculation still surrounds the effectiveness of topical application of glucosamine sulphate (GS) cream using massage to alleviate pain and slow down degenerative changes in patients with OA and it appears that there is inadequate data on the electromotive administration of glucosamine. However, it is unknown if electromotive force will drive in more GS to hasten pain relief and also reduce joint degenerative changes faster than massage, hence, this study is needed.

The primary aim of the study was to investigate the effect of GS IoT on selected radiographic parameters (JSW, inter-condylar thickening (ICT) tibia width, pain intensity, range of motion (ROM) and physical function in patients with knee OA. It was hypothesized that there would be no significant difference in the selected radiographic parameters, pain intensity, ROM and physical activity of patients with knee OA among patients who received GS through cross-friction massage

(CFM) only, IoT only; and a combination of both CFM and IoT in administering GS.

Methods

Participants

The 53 participants were patients with knee osteoarthritis, receiving treatment at the Out-Patient Physiotherapy Clinic of a Nigerian University Teaching Hospital in South West Nigeria.

Research design

This study was a randomized controlled trial (pre-test and post-test) experimental design.

Inclusion and exclusion criteria

The major inclusion criteria were that the participants must have knee OA with history not less than three months. There must also be radiological evidences of grade III on Kellegren classification. Excluded from the study were patients with history of knee surgery or replacement, patient with neuromuscular and musculoskeletal diseases; cardiac disorder, those using cardiac pacemaker, on intra articular steroid therapy within two months before the commencement of this study and participants with impaired skin sensation.

Sampling techniques

A total of 60 participants were recruited for the study with 20 in each group using purposive sampling technique. The sample size for this study was predetermined considering standard normal deviation to be 1.96, 0.02° of accuracy, power estimate of 80% and knee OA prevalence of 60% in adults. The probability of Type I error is considered as level of significance. The sample size was computed to be 18 participants per group but to give room for attrition, 20 participants were recruited for each group totaling 60 participants for the study. They were randomly assigned to three groups using fish bowl technique. Sixty separate slips, labeled groups 1, 2 and 3 with 20 for each group were mixed and pooled into a box. Each patient was instructed to pick a slip without looking into the box. Whatever group was picked would be the group that the patient was allotted. The flow chart is presented in Fig. 1.

Instruments

The instruments and test items included bathroom weighing scale, a modified height meter, an electrical stimulator (Model: Endomed 582, India), 70% alcohol and GS cream (glucosamine 8% w/w), (Urah). Amongst the test items are the following: a 10-point visual analogue scale (VAS), a plastic semi-circle Goniometer (Model E-Z ReadTM), Western Ontario and Mcmaster University — WOMAC OA index Questionnaire, X-ray film report, pointing divider, Vernier caliper and magnifying lens (Roger Bacon, Model No AC099).

Procedure for data collection

Ethical approval was obtained from the Health Research and Ethics Committee, Institute of Public Health, Obafemi Awolowo University, Ile Ife. All the patients consented to participate in the study. Participants in group 1 (IoT) received only 1 g (2 Finger-Tip Unit (FTU)) of GS cream which was administered via IoT. Group 2 (CFM) participants also received 1 g (2 FTU) of GS only, but it was administered using CFM while group 3 (combined therapy (CoT)) participants had interventions using 1 g of GS cream through both IoT and CFM.

A 10-point VAS was used to rate the pain. The VAS had been established to be reliable and effective in assessing knee pain arising from OA.[17] Pain intensities were rated on three occasions: on active and passive knee flexions, and on patellar grinding. The active knee flexion was measured in prone lying position using a standard procedure. Physical function was assessed using the WOMAC OS Questionnaire.[18] The physical function sub-scale was used to assess functional abilities of patients in this study. There are 17 items on the physical function sub-scale, it was rated on a 5-point Likert scale, ranging from 0 to 4 whereby "0 = none and "4 = extreme". The minimum obtainable score was "0" indicating best physical function while the maximum obtainable was "68" indicating poor physical function. The obtained score for physical function was divided by total possible score and multiplied by 100 and reported in percentage. Lower value depicts better physical function performance.

The JSW and inter-condylar thickening (ICT) were measured using standard procedures adopted by Deep *et al.*[19] and Lequesne.[20] The JSW was also measured manually using the method described by
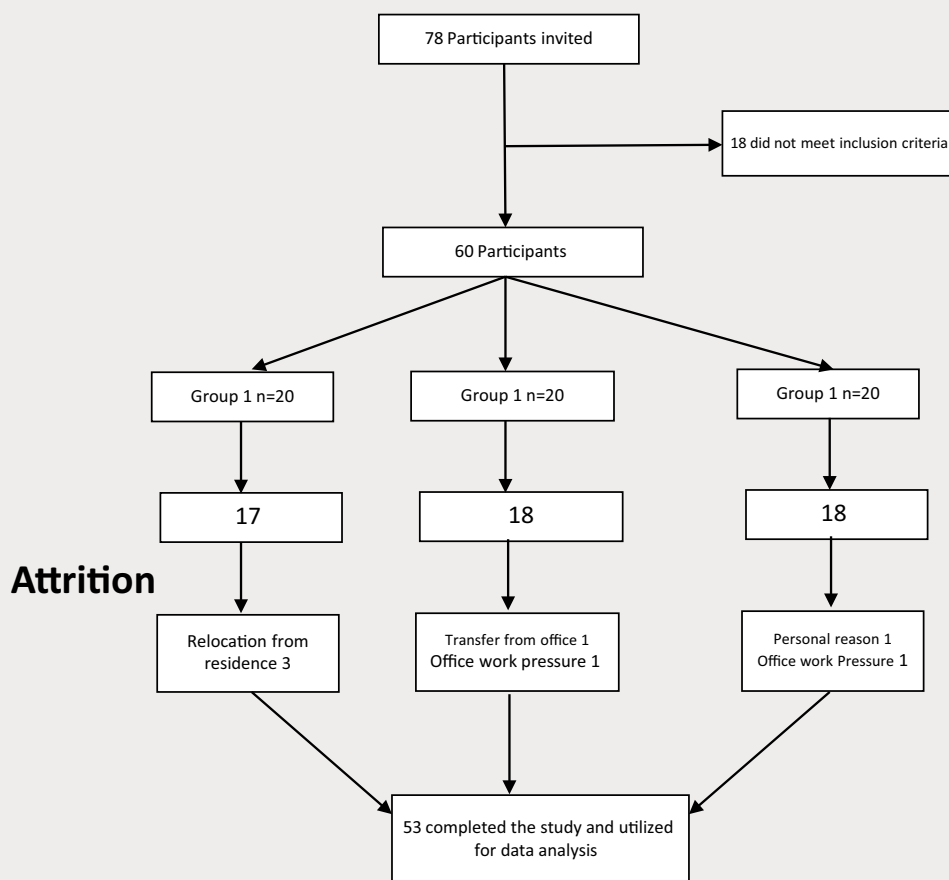
Fig. 1.   Flowchart for recruitment.

Lequesne.[20] Using the anteroposterior view of the X-ray film of each patient, the horizontal distance between the superior tip of the lateral and medial condyles of the tibial was divided into two while the lateral JSW was measured at the mid point of the first half and the medial JSW was measured at the mid point of the second half. The dividing pointer was used to prick the two inter-bone distances on the radiograph with the aid of a magnifying lens and then pricked a sheet of paper. The caliper was used to measure the inter-bone distance between the pricks.[20] The ICT on the X-ray film was measured manually as the distance between the tip of the anterior and posterior margins of the inter-condylar eminence used the method described by Lequesne, and the points of the caliper were used to measure inter-margin distance with the aid of a magnifying lens. The tibia width was measured from the superior tip of the lateral tibia condyle to that of the medial horizontally using pointing

divider and vernier caliper with the aid of magnifying lens. Prior to this, the reliability of the method was determined by using five X-ray films of patients with knee OA. The test–re-test interval was one week. The Pearson's product moment correlation reliability coefficiency obtained for the method of measuring the tibial width was found to be 0.87.

About 1 g of GS was placed on positive electrode (being positively charged) for patients in the IoT group.[21,22] An electrical stimulator machine (Model: Endomed 582, India) was used to deliver GS through the skin with the aid of electrodes. The Galvanic current mode in the Electrical Stimulator (Endomed 582) was used. The dose applied was 2 mA-min (2 mA × 20 min) for each subject in groups 1 and 3.[23] The active (positive) electrode was placed on the side where the participants experienced higher pain intensity (that is medial or lateral side of the knee joint). The pain intensity

was ascertained using valgus and varus ligamentous stress tests; and appley's compression tests. The skin areas where electrodes were fastened were cleansed with methylated spirit (70% alcohol) to minimize the risk of burns.[24] Transarthral electrode placement technique was used. The indifferent electrode was placed on the opposite side for subject in groups 1 and 3. Both electrodes were held in place by an adhesive strap. Each subject had intervention(s) twice a week for 12 weeks.

The intention-to-treat (ITT) principle was adopted in this study but last data measured were not carried forward for the seven patients that dropped out because the attrition happened in the first and second weeks of the protocols. We observed that the recorded data at the time of termination did not differ from the values obtained at baseline, hence, they were excluded from data analysis. The rate of attrition was almost uniform in three groups and the drop-out was not due to increase in severity, symptoms, group assignment or drug side effects. However, all the patients were followed up for another six weeks after the end of the study.

Data analysis

Descriptive statistics were used to summarize the data obtained. Levene's test was used to compare the homogeneity of age, weight, height and body mass index (BMI) across the groups. Repeated Analysis of Variance (ANOVA) was used to compare pain intensity, knee ROM, and selected radiographic parameters across the groups. It was also used to compare within group values at baseline, 6 weeks and 12 weeks. Where between groups, variance was observed at baseline, Analysis of co-variance was used to compare the differences. Post-hoc analysis (LSD) was used to determine the trend of differences in the groups. Kruska–Wallis test was used to compare physical functions across the three groups. Alpha level was set at $p = 0.05$.

Results

The result showed that eight (47.1%) of the participants who received GS IoT only have right knee OA and two (11.8%) are male. The affected sides for other groups are in Table 1. The age and

Table 1. Gender and distribution of affected sides of patients in the three groups.

Groups			N	%
IoT	Gender	Male	2	11.8
		Female	15	88.2
	Affected knee	Right	8	47.1
		Left	9	59.9
CFM	Gender	Male	4	22.2
		Female	14	77.8
	Affected knee	Right	10	55.6
		Left	8	44.4
CoT	Gender	Male	4	22.2
		Female	14	77.8
	Affected knee	Right	7	38.9
		Left	11	61.1

Note: 1 = IoT group, 2 = CFM group and 3 = CoT group.

selected anthropometric parameters of patients in IoT, CFM and CoT are presented in Table 2. The Levene's test for homogeneity showed that there was no significant difference in the selected anthropometric parameters.

Comparison of radiographic parameters of participants across the groups at baseline, 6th and 12th weeks

The means of JSW on medial side of the knee in the IoT group were 0.54 ± 0.08, 0.55 ± 0.07 and 0.59 ± 0.09 at baseline, 6th and 12th weeks, respectively. There was no significant difference in the medial JSW across the three groups at baseline and 6th week, but there was significant difference at the 12th week. ($F = 6.00, p = 0.01$). There was significant difference in lateral JSW and ICT across the three groups at baseline ($F = 4.34, p = 0.02$). Other mean values are presented in Table 3. There was significant difference in lateral JSW across the three groups at baseline ($F = 4.34, p = 0.02$). At the 6th week, there were no significant differences in all the selected parameters. However, at the 12th week, there were significant differences in the medial and lateral JSW compared to baseline and 6th week ($F = 6.00, P = 0.01$ and $F = 12.32, p = 0.001$, respectively) (Table 3).

Table 2.   Comparison of anthropometric parameters and onset duration of participants across the three groups.

	IoT		CFM		CoT		Levene (p)
	Mean	SD	Mean	SD	Mean	SD	sig
Age	63.53	11.35	49.78	13.19	58.11	9.91	0.35
Weight	80.47	9.49	75.78	8.47	76.00	9.08	0.62
Height	1.52	1.61	0.96	0.49	1.63	0.86	0.73
BMI	35.57	4.13	29.55	4.01	28.39	4.76	0.93
Duration	11.47	7.80	8.72	6.17	11.11	7.28	0.26

Note: 1 = IoT group, 2 = CFM group and 3 = CoT group.
*Levene Test for Equality of Variances.

Table 3.   Comparison of radiographic parameters of all the participants at baseline, 6th and 12th weeks in the three groups.

		Group 1		Group 2		Group 3		F	P
		Mean	SD	Mean	SD	Mean	SD		
Medial JSW	Baseline	0.54	0.08	0.49	0.15	0.51	0.11	0.72	0.49
	6th week	0.55	0.72	0.52	0.17	0.51	0.10	0.49	0.62
	12th week	0.59	0.09	0.79	0.30	0.58	0.15	6.00	0.01
Lateral JSW	Baseline	0.82	0.14	0.73	0.17	0.68	0.11	4.34	0.02*
	6th week	0.81	0.17	0.82	0.26	0.11	0.68	2.73	0.08*
	12th week	0.84	0.16	0.57	0.18	0.68	0.13	12.32	0.001*
ICT	Baseline	1.05	0.39	0.94	0.19	1.08	0.36	3.97	0.03*
	6th week	1.19	0.39	0.94	0.19	1.02	0.31	2.99	0.06*
	12th week	1.24	0.42	0.94	0.19	1.13	0.35	3.60	0.04*
Tibia width	Baseline	6.71	1.38	7.47	0.62	6.84	1.09	2.54	0.09
	6th week	6.76	1.33	7.41	0.62	6.83	1.12	1.83	0.17
	12th week	6.66	1.34	7.42	0.61	6.78	1.13	2.57	0.09

*Analysis of co-variance.

The result of the post-hoc analysis (LSD) at baseline showed that there were no significant differences in the baseline parameters excluding the lateral JSW between CoT and IoT; and between ICT of participants in IoT and CFM groups (Table 4). The medial JSW of participants in CFM group was significantly higher than that of participants in IoT and CoT groups ($p = 0.005$ and $p = 0.004$, respectively) at the 12th week, (Table 5). The lateral JSW of IoT group was significantly higher than that of CFM group ($p = 0.001$) and that of CoT group ($p = 0.01$), but that of later was higher than that of the former ($p = 0.04$) (Table 5).

Comparison of pain intensity and ROM of participants at baseline, 6th and 12th weeks

The mean of pain intensity on active knee flexion was 4.94 ± 1.30 on a 10-point rating scale (VAS) for participants in IoT group (GS IoT) at baseline. The mean pain intensities on active knee flexion at 6th and 12th weeks are also presented in Table 6. The result of ANOVA showed that there were significant differences in pain intensities on active and passive knee flexion; and patellar grinding within the IoT group participants ($F = 43.00$, $p = 0.001$, $F = 53.54$, $p = 0.001$; and

Table 4. Result of post hoc (LSD) analysis of baseline radiographic parameters of all the participants across the three groups.

	I	J	Mean difference $(I - J)$	P
Medial JSW	1	2	0.05	0.24
		3	0.03	0.45
	2	3	0.02	0.67
Lateral JSW	1	2	0.84	0.08
		3	0.14	0.05
	2	3	0.06	0.24
ICT	1	2	0.31	0.01
		3	0.17	0.13
	2	3	−0.14	0.20
Tibia width	1	2	−0.76	0.08
		3	−0.14	0.70
	2	3	0.62	0.09

Note: 1 = IoT group, 2 = CFM group and 3 = CoT group.

$F = 12.81, p = 0.001$, respectively). The mean pain intensities on active and passive knee flexion; and patellar grinding for CFM and CoT groups are presented in Table 6. The post-hoc analysis (LSD) showed that the pain intensity on active knee flexion on a 10-point rating scale (VAS) at the 6th week of IoT group participants was significantly lower than that of baseline $(p = 0.001)$, with further decrease at 12th week $(p = 0.001)$. Similarly, the pain intensity on active knee flexion at 12th week for IoT participants was significantly lower than that of 6th week $(p = 0.001)$. The same

Table 5. Result of post hoc (LSD) analysis of radiographic parameters of all the participants across the three groups after 12th week.

	I	J	Mean difference $(I - J)$	P
Medial JSW	1	2	−0.20	0.005
		3	0.01	0.94
	2	3	0.21	0.004
Lateral JSW	1	2	0.27	0.001
		3	0.15	0.01
	2	3	−0.11	0.04
ICT	1	2	0.30	0.01
		3	0.11	0.32
	2	3	−0.18	0.10
Tibia width	1	2	−0.75	0.14
		3	−0.12	0.73
	2	3	0.63	0.08

Note: 1 = IoT group, 2 = CFM group and 3 = CoT group.

trends were observed on passive knee flexion and patellar grinding at 6th and 12th weeks, $(p = 0.001)$ (Table 7). The mean ROM (active knee flexion) was 107.35 ± 12.18 at onset for participants in the IoT group while at the 6th and 12th weeks, the mean of ROMs was 114.06 ± 10.80 and 122.94 ± 0.81, respectively. The result of ANOVA showed that there was significant difference in ROM within IoT group participants $(F = 9.11, p = 0.001)$ (Table 6).

For participants in the CFM group, the mean pain intensities on active and passive knee flexions were $4.72 \pm 2.22, 3.39 \pm 1.65$ and 1.83 ± 1.15, respectively, on a 10-point rating scale (VAS) at baseline, 6th and 12th weeks. The result of ANOVA showed that there were significant differences in pain intensities on active and passive knee flexions at baseline, 6th and 12th weeks within the CFM group participants $(F = 12.59, p = 0.001;$ $F = 15.55, p = 0.001,$ respectively) (Table 6). The post hoc analysis (LSD) showed that the pain intensity on active knee flexion at 6th week for CFM group participants was significantly lower than that of baseline $(p = 0.025)$ while at the 12th week, it was also significantly lower than at baseline $(p = 0.001)$. Similarly, the pain intensity on active knee flexion at 12th week for the CFM group was significantly lower than at 6th week $(p = 0.009)$. The result of post hoc analysis (LSD) showed that the ROM at 12th week of CFM group was significantly higher than that of baseline $(p = 0.001)$ (Table 8).

The result showing comparison of mean of pain intensities and ROMs for other groups are presented in Table 6. The result of the post hoc analysis (LSD) showed that the pain intensity on active knee flexion on a 10-point rating scale (VAS) at 6th week of CoT group participants was significantly lower than that of baseline $(p = 0.001)$ and also the pain intensity on active knee flexion on a 10-point rating scale (VAS) at 12th week in CoT group was significantly lower than that of baseline $(p = 0.001)$. Similarly, the pain intensity on active knee flexion on a 10-point rating scale (VAS) at 12th week in CoT group was significantly lower than that of 6th week $(p = 0.01)$. Other post hoc analysis (LSD) results are shown in Table 9.

There was significant difference in pain intensity on active knee flexion on a 10-point pain rating scale across the three groups (VAS) $(F = 9.33, p = 0.01)$ and same trend was found for passive

Table 6.   Comparison of pain intensity and ROM of participants at baseline, 6th and 12th weeks within the groups.

| | | | Baseline | | 6th week | | 12th week | | | |
			Mean	SD	Mean	SD	Mean	SD	F	P
IoT	Pain intensity	OAKF	4.94	1.30	2.94	0.97	1.77	0.66	43.00	0.001*
		OPKF	6.41	1.33	3.77	0.97	2.94	0.66	53.54	0.001*
		OPG	3.88	1.50	1.88	1.32	2.24	0.75	12.81	0.001*
	ROM	OAKF	107.35	12.18	114.06	10.80	122.94	8.81	9.11	0.001*
CFM	Pain intensity	OAKF	4.72	2.22	3.39	1.65	1.83	1.83	12.59	0.001*
		OPKF	5.83	1.98	4.00	1.65	2.83	1.15	15.55	0.001*
		OPG	3.83	1.58	3.33	1.09	3.00	0.91	2.11	0.130
	ROM	OAKF	104.22	17.25	113.89	14.24	121.61	10.18	6.78	0.002*
CoT	Pain intensity	OAKF	6.83	1.02	3.39	1.04	2.50	0.92	93.79	0.001*
		OPKF	7.33	1.37	4.12	1.15	3.06	1.06	61.58	0.001*
		OPG	5.67	1.65	3.39	1.38	2.56	0.78	26.84	0.001*
	ROM	OAKF	97.33	14.38	102.28	10.25	116.00	11.69	11.27	0.001*

Notes: *Significant at $p < 0.05$.
OAKF: On Active Knee Flexion, OPKF: On Passive Knee Flexion, OPG: On Patellar Grinding, 1 = IoT, 2 = CFM and 3 = CoT.

Table 7. Post hoc analysis (LSD) of pain intensity and ROM of all the participants at baseline, 6th and 12th weeks within IoT group.

		I	J	Mean changes (I − J)	P-value
Pain intensity	OAKF	1	2	2.00	0.001*
			3	3.18	0.001*
		2	3	1.18	0.001*
	OPKF	1	2	2.65	0.001*
			3	3.47	0.001*
		2	3	0.82	0.020*
	OPG	1	2	2.00	0.001*
			3	1.65	0.001*
		2	3	−0.35	0.410
ROM	OAKF	1	2	−6.71	0.070
			3	−15.59	0.001*
		2	3	−8.88	0.020*

Notes: *Significant at $p < 0.05$.
1 = Baseline, 2 = 6th week and 3 = 12th week, OAKF: On Active Knee Flexion, OPKF: On Passive Knee Flexion, OPG: On Patellar Grinding.

Table 8. Post hoc analysis (LSD) of pain intensity and ROM of all the participants at baseline, 6th and 12th weeks within CFM group.

		I	J	Mean changes (I − J)	P
Pain intensity	OAKF	1	2	1.33	0.030*
			3	2.89	0.001*
		2	3	1.56	0.001*
	OPKF	1	2	1.83	0.001*
			3	3.00	0.001*
		2	3	1.17	0.040*
	OPG	1	2	0.50	0.230
			3	0.83	0.050*
		2	3	0.33	0.420
ROM	OAKF	1	3	−9.67	0.050*
			3	−17.34	0.001*
		2	3	−7.72	0.110

Notes: *Significant at $p < 0.05$.
1 = Baseline, 2 = 6th week and 3 = 12th week, OAKF: On Active Knee Flexion, OPKF: On Passive Knee Flexion, OPG: On Patellar Grinding.

knee flexion and patellar grinding at baseline for participants in the three groups (Table 10). The post hoc analysis (LSD) showed that the pain intensity on active knee flexion for IoT group participants was significantly lower than that of CoT group ($p = 0.001$) and CFM group ($p = 0.001$). Similar trends were also observed for passive knee flexion and on patellar grinding (Table 11).

Comparison of physical function of participants across the three groups at baseline, 6th and 12th weeks

The physical function of participant in IoT group at baseline was 28.31 ± 6.19 on a WOMAC scale.

Table 9. Post hoc (LSD) analysis of pain intensity and ROM of all the participants at baseline, 6th and 12th weeks within CoT group.

		I	J	Mean changes (I − J)	P
Pain intensity	OAKF	1	2	3.44	0.001*
			3	4.33	0.001*
		2	3	0.89	0.010*
	OPKF	1	2	3.17	0.001*
			3	4.28	0.001*
		2	3	1.11	0.008*
	OPG	1	2	2.28	0.001*
			3	3.11	0.001*
		2	3	0.83	0.060
ROM	OAKF	1	2	−4.94	0.230
			3	−18.67	0.001*
		2	3	−13.72	0.001*

Notes: *Significant at $p < 0.05$.
1 = Baseline, 2 = 6th week and 3 = 12th week, OAKF: On Active Knee Flexion, OPKF: On Passive Knee Flexion, OPG: On Patellar Grinding.

The physical functions of participants in the CFM and CoT groups are presented in Table 12. The result of Kruskal–Wallis showed that there were significant differences in physical function among the participants across the three groups at baseline ($H = 4.97$, $p = 0.01$). The physical functions of participants in IoT, CFM, CoT groups at the 6th week are presented in Table 12. There were also significant differences in physical functions among the participants across the three groups at 6th and 12th weeks ($H = 9.19$, $p = 0.01$; $H = 3.23$, $p = 0.01$, respectively) (Table 12).

Discussion

Topical delivery of medication permits the avoidance of first pass metabolism by the liver and it also by-passes the gastric system providing higher levels and quicker tissue saturation.[11,25] It is widely acknowledged that transdermal delivery improves patient compliance.[25] Levene's test was used to determine if the three groups have equal variances. Comparability across samples is called homogeneity of variance. The result of Levene test in this study confirmed that the anthropometric parameters of patients in the three groups were comparable in age, weight, height and (BMI), hence differences observed in this study could not be attributed to the parameters. Chronicity of diseases could also affect the outcome of interventions, however, there was no significant difference in the duration of onset of knee OA of patients in the three groups.

Measurement of changes in JSW is currently the gold standard in evaluation of structured modifying drugs in OA.[26] This current study evaluated both medial and lateral JSWs because OA may

Table 10. Comparison of pain intensity and ROM of all the participants across the three groups after 12th week.

		IoT		CFM		CoT			
		Mean	SD	Mean	SD	Mean	SD	F	P
Pain intensity	OAKF: Base	4.94	1.30	4.72	2.22	6.83	1.04	9.34	0.001*
	6th	2.94	0.97	3.39	1.65	3.35	1.06	0.66	0.520
	12th	1.76	0.66	1.83	1.15	2.50	0.92	3.33	0.040*
	OPKF: Base	6.41	1.33	5.83	1.98	7.33	1.37	4.07	0.020*
	6th	3.77	0.97	4.00	1.65	4.12	1.17	0.33	0.720
	12th	2.94	0.66	2.83	1.15	3.06	1.06	0.23	0.780
	OPG: Base	3.88	1.50	3.83	1.58	5.67	1.65	7.84	0.001*
	6th	1.88	1.32	3.33	1.09	3.35	1.41	7.51	0.001*
	12th	2.23	0.75	3.00	0.91	2.56	0.78	3.86	0.030*
ROM	AKF: Base	107.35	12.18	104.22	17.25	97.33	14.38	2.12	0.130
	6th	114.06	10.80	113.89	14.24	01.53	10.04	6.27	0.004*
	12th	122.94	8.81	121.61	10.18	116.00	11.69	2.26	0.120

Notes: *Significant at $p < 0.05$.
OAKF: On Active Knee Flexion, OPKF: On Passive Knee Flexion, OPG: On Patellar Grinding, Base: Baseline.

Table 11. Post hoc (LSD) analysis of pain intensity and ROM of all the participants across the three groups at baseline.

		I	J	Mean changes (I − J)	p
Pain intensity	OAKF	1	2	2.19	0.690
			3	−1.89	0.001*
		2	3	−2.11	0.001*
	OPKF	1	2	0.58	0.290
			3	−0.92	0.090
		2	3	−1.5	0.010*
	OPG	1	2	0.05	0.930
			3	−1.78	0.002*
		2	3	−1.83	0.001*
ROM	OAKF	1	2	3.13	0.530
			3	10.01	0.050*
		2	3	6.89	0.170

Notes: *Significant at $p < 0.05$.
1 = IoT, 2 = CFM, 3 = CoT, OAKF: On Active Knee Flexion, OPKF: On Passive Knee Flexion, OPG: On Patellar Grinding.

involve either medial and lateral tibiofemoral or patellafemoral compartments according to the localization of cartilage deterioration.[27] At baseline, the three groups were comparable in medial joint space and tibial widths. At the 6th week, there were no significant changes in all the radiographic parameters. However, at the 12th week (after three months), there were diffused effects of different interventions on JSWs. There was significant increase in the medial joint space when massage was used to administer GS cream while there was a significant increase in lateral joint space when GS cream was administered through the process of IoT. The combined therapies improved the lateral joint space that makes use of CFM technique only. In knee OA, tight muscle increases the compression of joint while tightening of quadriceps, hamstring and calf muscle results in poor coordination and slower reaction time.[28] The tightening of quadriceps, hamstring, calf muscle and poor flexibility associated with knee OA may likely have a combined closing effect on the 1knee joint space. The administration of GS cream through massage might have loosened and relaxed soft tissues at the knee joint; and these might be the reason for the increased medial joint space at the knee joint. The use of massage is an age-old process that involves stimulations of tissues by rhythmically applying both stretching and pressure.[29]

CFM had been reported to stimulate blood flow and also breaks down cross-bridge; and the frictional pressure is applied at right angle thereby stretching apart the musculo-tendinous tissues.[30] The stretching and pressure at the knee joint might improve the flexibility of the quadriceps and hamstring muscles which subsequently open up the joint space of the knee in patients with OA. Flexibility is related to the extensibility of musculo-tendinous units that cross a joint. Onigbinde et al.[31] reported that transdermal massage of glucosamine was very effective in improving hamstring flexibility and increasing knee flexion ROM among patients with knee OA. The reported improvement in medial joint space might be attributed to the contributions of the manipulative effects of CFM and transdermal application of GS cream which both improve flexibility. This study corroborated that of Reginster et al.[32] who also observed an increase in the JSW in patients with OA. Also, Dahmers and Schiller[33] reported the increase in medial compartment of tibia femoral joint space following the administration of GS after 12 weeks of

Table 12. Comparison of physical function of participant across the three groups at baseline, 6th and 12th weeks.

	Physical function						
	IoT Mean ± SD		CFM Mean ± SD		CoT Mean ± SD		H	P
Baseline	28.31	6.19	34.08	10.82	37.96	9.50	4.97	0.010*
At 6th week	17.85	4.98	22.70	5.83	23.37	6.64	9.19	0.010*
At 12th week	11.27	2.64	16.61	6.63	14.82	8.23	3.23	0.010*

Notes: *Significant at $p < 0.05$.
IoT: iontophoresis, CFM: cross-friction massage, CoT: combined therapy.

intervention. Also, in a recent study, Durmus et al.[34] evaluated the effect of GS on the cartilage repair, and found an increase in the medial JSW.

This study observed that at baseline, the ICT of patients who had intervention using CFM was significantly lower than that of those who received GS IoT only at baseline, however, after 12 weeks of intervention, the ICT remained lower for the former. There was no significant difference in the tibia width across the three groups at baseline, 6th and 12th weeks. This implied that there was no progression in the degeneration of bone margins of the tibia condyle after three months. The within groups assessment showed that knee OA patients who received GS via CFM only had increased lateral JSW at 12th week than at baseline. Also, the lateral JSW at 12th week was significantly higher than that at baseline and 6th week. The significant increase in the medial and lateral JSW of the knee joints corroborated the findings of Reginster et al.[32] This study observed no significant difference in the medial JSW, lateral JSW, ICT and tibia width of patient who received GS IoT only and similar trend was observed for patients who had both glucosamine through IoT and massage. The clinical implication of this is that there was neither regression nor progression in degenerative changes in the radiographic features of patients who received either IoT only or combined interventions. Besides, it is also suggestive of the importance of using plain radiograph to monitor progress made in the management of knee OA using JSW, ICT and tibia width as indices for outcome measures.

This study rated pain intensities on active and passive movements; and during patellar grinding. It was observed that after 12 weeks of interventions, the administration of glucosamine via IoT significantly reduced the pain intensity on active knee flexion and patellar grinding. The pain intensity experienced by patients who had CoT was significantly higher at baseline compared to that of those who received massage only. However, after 12 weeks, there was no significant difference between levels of intensities between the groups. This implied that combination of GS IoT and massage was more effective in managing pain associated with knee OA. This corroborated the reported decrease in pain intensity of patient with knee OA after administration of GS.[22,26] This current study further lent credence to the effectiveness of administration of GS in alleviating pain in patient with knee OA as reported by Graig.[26] and

Reginster et al.[32] Furthermore, Onigbinde et al.[11] reported that the administration of 1 g of GS cream was effective in alleviating pain experienced by knee OA patients. GS IoT has been severally observed to modulate and significantly reduce pain immediately after use.[11,35]

There was significant increment in knee flexion at six weeks of interventions across the groups. However, after 12 weeks of intervention, there was no significant difference in the ROMs. This implied that patients who had CoT might have reached a plateau in ROM at the 12th week. This current finding supported the report of Onigbinde et al. who observed that patients who had GS IoT had significantly better active knee flexion compared with those who had the topical medication through massage because the duration of their intervention was also within six weeks.[11] However, within the groups, there was significant increase in active knee flexion. This is in consistent with findings of Onigbinde et al. who also reported that there was an increase in the ROM of patient with knee OA following the administration of GS.[22]

OA of the knee is the most common cause of chronic disability among the elderly worldwide.[36] The degree of flexibility of the quadriceps and hamstring group of muscles contributes to smooth and precise ambulatory functions. Most subjects with OA usually experience functional limitations in activities of daily living.[37] The current findings on physical functions showed that after 12 weeks of intervention, there was significant improvement across the groups, but participants in the IoT group showed improved physical function compared to the other groups. This corroborated the previous study that showed that GS alleviates pain and subsequently improves the physical functions of patients.[22] Also, Braham et al. reported that glucosamine supplementation provides degree of pain relief and further improved the function in persons who experience regular knee pain, which may be caused by prior cartilage injury and/or OA.[22,38]

Conclusion

We concluded that at the 12th week, there were significant decreases in the degenerative changes at the knee joints of patients with knee OA. The administration of GS using IoT alone significantly increases the lateral JSW than other interventions while CFM only significantly increases the medial JSW. However, none of the three interventions was

superior in their effects on ICT and degeneration of tibia bone margin after 12 weeks. Also, GS administration through CFM alleviated pains, increased active and passive knee flexion better than the use of IoT alone or combination of both interventions. Furthermore, the administration of GS using IoT only increased the physical functions than CFM or combination of both interventions.

Conflict of Interest

There was no conflict of interest in this study.

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Author Contributions

Onigbinde Ayodele Teslim contributed in developing the concept, data collection and analysis, script preparation, revising the manuscript and editing. Owolabi Adegbenga Rotimi contributed to data collection, analysis, script preparation, revising the manuscript and editing. Lasisi Kamil contributed to data collection, analysis, script preparation, revising the manuscript and editing. Sarah Oghenekewe Isaac contributed to data collection, script preparation and editing. Ibikunle Adeoye Folorunso contributed to data collection, script preparation and editing.

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