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Research Article

CLINICAL EFFECTIVENESS OF GLUCOSAMINE SULFATE, CHONDROTIN SULFATE, METHYLSULFONYLMETHANE PHONOPHORESIS IN KNEE OSTEOARTHRITIS

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A B S T R A C T

Background and purpose: Phonophoresis was believed to influence drug delivery by increasing cell permeability, causing particle oscillations within the tissue and drug milieu. This trial was designed to investigate the effect of Glucosamine sulfate, chondroitin sulfate and Methylsulfonylmethane Phonophoresis (PH) in knee osteoarthritis (OA).

Basic methods: Seventy patients OA allocated randomly into three groups, PH group, Topical group, and control group. Participants in the three groups received hamstrings and calf muscles stretch, and isometric strengthening of the quadriceps, 3 sessions per week for 12 successive weeks. Pain, active ROM, and function were assessed before and after 12 weeks.

Main results: PH group reported higher improvement of pain, ROM and functional disability. Overall effect yielded significant difference between groups regarding pain ($F=194.7$, $P<0.0001$), ROM ($F=74.53$, $P<0.0001$), and functional disability ($F=124.95$, $P<.0001$). A significant difference of pain, ROM and functional disability was found between PH vs topical application, PH vs control.

Principal Conclusion: Glucosamine sulfate, Chondroitin sulfate and Methylsulfonylmethane phonophoresis is superior to topical application for the short term treatment of knee osteoarthritis. It provided statistically significant improvements in pain, neck ROM and functional disability in knee OA.

INTRODUCTION

Glucosamine and chondroitin has been widely used since a long time for treatment of symptoms of osteoarthritis (OA). They were used as a prescription drugs in continental Europe, but they are less regulated dietary supplements in the United States and Great Britain. Glucosamine sulfate (GS) was proved to be effective in reducing pain and other OA symptoms when it was compared to a placebo [1,2] On the other side, Rindone *et al*. found no difference in knee pain between GS and a placebo [3]. This symptom modification is sustained for years, and there is an intriguing suggestion of possible disease (structure) modification [4,5]. These long-term effects are particularly relevant [6], given the chronic and progressive nature of this degenerative joint disease. GS may potentially delay joint structure changes in OA [4,5].

The combination of GS and CS were suggested to be effectives in the management of OA. Glucosamine, chondroitin, and manganese ascorbate significantly improved pain in adults with knee OA [7,8]. Glucosamine was used in combination with MSM for treating OA. They produced an analgesic and anti-inflammatory effect. Combination therapy showed better efficacy in reducing pain and swelling and in improving the functional ability of joints than the individual agents [9].

Glucosamine sulfate and CS were administered orally, or by intravenous injection, or topically. Topical application of glucosamine and chondroitin sulfate is effective in relieving the pain from OA of the knee and improvement is evident within 8 weeks [10]. Topically applied drugs can induce local and systemic effects that can be distinguished by examining local tissue drug concentrations (under the site of application) and blood or urine level. Topically applied drugs with particularly systemic effects diffuse through the epidermis to the dermis to reach the capillary network. Drugs with local targets diffuse into the area immediately below the administration site, such as subcutaneous tissue, muscle, synovium, ligaments, tendons, and joints [11].

Phonophoresis (PH) was known to enhance penetration of any medication through the normal skin by ultrasound irradiation. It can be obtained with the medication gel or cream either used as a coupling medium for the ultrasound head or with any regular coupling gel, the actual medication gel or cream being applied on the irradiated area immediately thereafter [12]. PH was believed to influence drug delivery by increasing cell

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permeability, causing particle oscillations within the tissue and drug milieu, and perhaps inducing drug molecule motion through radiation pressure forces. The most likely mechanical explanation is thought to be intercellular diffusion from high-speed vibration of drug molecules along with vibration of the cell membrane and its component [13].

Many trials were attempted to investigate the effect of PH with different drugs in the treatment of OA. It was used with ibuprofen [14], ketoprofin [15], dexamethasone sodium phosphate [16], and piroxicam [17]. Drug PH was proved to be effective in pain relief and improvement of patient's symptoms and function. Therefore, the purpose of this study is to examine the effectiveness of the transdermal transfer of GS, CS and MSM by ultrasound on pain, active knee flexion ROM and the functionality of the knee joint.

METHODS

Trial Design and Participants

The study is a randomized controlled trial (RCT). Seventy patients with knee OA (male and female) participated in the study. Their ages was >50 years. They were randomly assigned into 3 groups, 2 experimental groups and a control group. PH group: Consisted of 25 patients, they received GS, CS and MSM gel phonophoresis with pulsed ultrasound therapy (50% duty cycle),1 MHZ, 1.5 w/cm2, 5 min according to Cagnie, *et al* 2003 [15]; plus a traditional exercise program that included stretching exercises of the hamstrings and calf muscles through straight leg raising (SLR) of the knee with ankle dorsiflexion, and isometric strengthening of the quadriceps. Topical group: Consisted of 22 patients, they received topical application of GS, CS and MSM gel plus the traditional exercise program by means of sham US ((50% duty cycle),1 MHZ, 1.5 w/cm2, 5 min). Control group: Consisted of 23 patients, they received only the traditional exercise program. The treatment was given 3 sessions/week for 12 successive weeks.

The participants were selected randomly from the out clinic of faculty of physical therapy and from the orthopedics outpatient's clinic, faculty of medicine, Cairo University. Over several months at those clinics hundreds of patients came in to be examined for regular medical problems. 78 patients who were examined by orthopedists for knee OA problems consented to enter the study. These patients were assessed by the orthopedists on staff for eligibility to the study according to the inclusion and exclusion criteria. 70 patients were determined to meet the study criteria and were enrolled into the study. The 70 selected patients were assigned to PH sessions or topical application with Sham US or a traditional exercise program (Figure.1).

All participants provided written informed consent according to declaration of Helsinki to participate in our study, few participants agreed to put the images taken for them during treatment in this paper. The Board Council of Higher Education of the School of Physical Therapy, the Institutional Review Board of Higher Education and Research of Cairo University, and the Supreme Council of Universities at Egypt approved our study (NO:/ P.T.REC/012/001348).

Inclusion and Exclusion Criteria

Eligibility was defined as symptomatic knee OA for at least 6 months according to the clinical criteria of the American College of Rheumatology (ACR) [18] and radiographic confirmed knee OA according to the Kellgren & Lawrence scale [19]. Exclusion criteria included acute septic arthritis; inflammatory arthritis; any other type of arthritis; history of knee buckling or recent knee injury; lack of physical or mental ability to perform or comply with the treatment procedure; diabetes mellitus; fibromyalgia or other chronic pain syndromes; concurrent anti-coagulant/anti-platelet drugs; arthroscopy or intra-articular injections in the previous 3 months. Patients using other arthritis therapies (CAM, etc.) and patients using NSAIDs were required to undergo a 10-day washout period before enrollment.

Sample size

The sample size calculations were performed using the G*Power software (version 3.0.10). F-test MANOVA with global effects was selected. Pain was chosen as the primary outcome measure. The effect size of pain was estimated to be medium (0.25). Considering a power of 0.95, an α level of 0.05, 3 groups and response variables of 2, a generated sample size of at least 14 participants per group would be required. Allowing for a 20% dropout rate, it was necessary to reach a total sample level of a minimum of 70 participants.

Randomization

The study was a 12-week randomized controlled trial by using random numbers. Immediately after the baseline evaluation, participants were randomly assigned to receive GS, CS, SMS PH, topical GS, CS, SMS SUS and a control group. Randomization was implemented simply by means of a computer-generated randomized table using the SPSS program (IBM, USA) prepared in advance to data collection. A specific identification number was assigned for each participant. These numbers were randomized into three groups. Individual and sequentially numbered index cards were secured in opaque envelopes. Each participant was given a hand-picked envelope and was relocated accordingly to their treatment groups. Participants did not know to which group they were assigned and which treatment would be given.

Evaluation

Outcome measures

study were the visual analogue scale (VAS) for pain assessment, the modified electro-goniometer for knee flexion ROM assessment, and the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index for functional disability of the knee joint.

Assessment of knee pain

The VAS is a subjective measurement that the patient reports on a 10 cm horizontal line, where 0 indicates no pain and 10 the worst pain, it is particularly useful in assessing changes in pain for individuals receiving therapy [20].

Assessment of knee ROM

Penny and Giles electrogoniometer (Penny and Giles Biometrics Ltd, Gwent, UK) was attached by double-sided tape to the lateral aspect of the thigh and lower leg. To allow the goniometer to be positioned accurately during assessment, the subjects were marked with ink at the center of the lateral femoral condyle and then 7 (cm) above and below that point on the line connecting the greater trochanter of the hip to the head of the fibula. The mechanical signals from the measuring

element in the end-blocks were converted into a digital signal by a data log acquisition unit which connected the electrogoniometer to a display unit [21].

Assesement of Proprioception Accuracy

Isokinetic dynamoter, 3 multi-joint testing and rehabilitation system (Biodex medical system, Shirley, NY, USA); one of the advanced isokinetic systems that was used to quantify the proprioceptive acuity in knee joint. Initially, the participant's knee was flexed at right angle for each trial. Then the participant's leg was then moved passively to the test angle of 45° of knee flexion by the experimenter with an angular velocity of 4°/sec. Knee flexion at 45° was sustained for 3 seconds. The experimenter passively brings back the participants' leg to the starting position. This process was repeated twice for familiarization with the test. After five second rest period; the dynamometer passively took the participant's leg at 45° of knee flexion at an angular velocity of 2°/s. The participants were informed to press a stop button when they feel they reached the prescribed angle. The machine recorded the amount of error in the participant's trial to match the reference angle [22].

Assessment of knee function

The WOMAC consists of 24 points that includes pain, stiffness, and physical function. Scoring and interpretation ranged from 0 to 5. 0=none response, 1=slight, 2=moderate, 3=severe, 4=extreme [23,24].

Treatment protocol

Glucosamine Sulfate, Chondroitin Sulfate and MSM Phonophoresis

For PH group, pulsed ultrasound was used with frequency 1 MHz, intensity 1.5 W/cm², and (50% duty cycle) for 5 minutes /session. Drugs concentrations in gel were: GS 30mg/g CS 50mg/g and MSM 10mg/g gel were put on ultrasound head before application. Topical application was done by applying of GS, CS and MSM gel on the head of US and moving it on the knee for 5 minutes with US where the device is off and all controls on zero.

The Traditional Exercise Program

The traditional exercise program in the form of: 1) Stretching of the hamstring muscles from supine lying position for 3 successive times, 30 seconds each with rest for 1 minute in between stretches, 2) Stretching of the calf muscles from supine lying position for 3 successive times, 30 seconds each with rest for 1 minute in between stretches [25], 3) Straight leg raising exercise in which the patients were positioned in the crook lying position with the unexercised limb is the flexed one then the patients was asked to contract the quadriceps muscle and elevate the limb to 45º and hold for 6 seconds, slowly lower the limb and then relax for 6 seconds, three sets of 10 repetitions were be done [26], 4) Isometric strengthening of the quadriceps muscle in the form of 3 sub maximal isometric contractions of increasing intensity followed by 6 maximal 5 seconds isometric contractions, the isometric contractions were repeated at multiple knee angles (30º–60º–90º) degrees respectively, each contraction was followed by 30 seconds rest period and each set of contractions at each knee angle was followed by 1 minute rest [27].

Statistical Analysis

Data were analyzed for this randomized controlled trial using descriptive statistics and with a 3×2 mixed design MANOVA with the treatment groups (2 experimental vs. control) used as the between subjects factor and time of assessment (baseline, after treatment) used as the within subjects factor. The software used for statistical analysis was the SPSS version 20. The P-value was set at 0.05. The dependent variables were VAS scores, Knee flexion ROM and WOMAC index scores. Before data analysis, Shapiro–Wilk test was used to test the normality of the data and Levene's test was used to test the equality of variances. The differences in demographic characteristics for both groups were assessed using one way ANOVA test. A preliminary power analysis with a power 80% determined a sample size of 25 participants in each group.

RESULTS

Table 1 lists the general physical characteristics of the 70 participants included in our study. PH group consisted of 25 participants; 13 females (52%) and 12 females (48%), Topical group consisted of 23 participants; 14 females (60.94%) and 9 males (39.06%); and Control group consisted of 22 participants; 13 females (59.9%) and 9 males (13.9%). As indicated by the one-way analysis of variance (ANOVA), there were no significant differences in the mean values of age, gender, weight, height and body mass index among the three groups with a P value > 0.05. Person chi-square test showed no significant difference of sex between groups (p = 0.186).

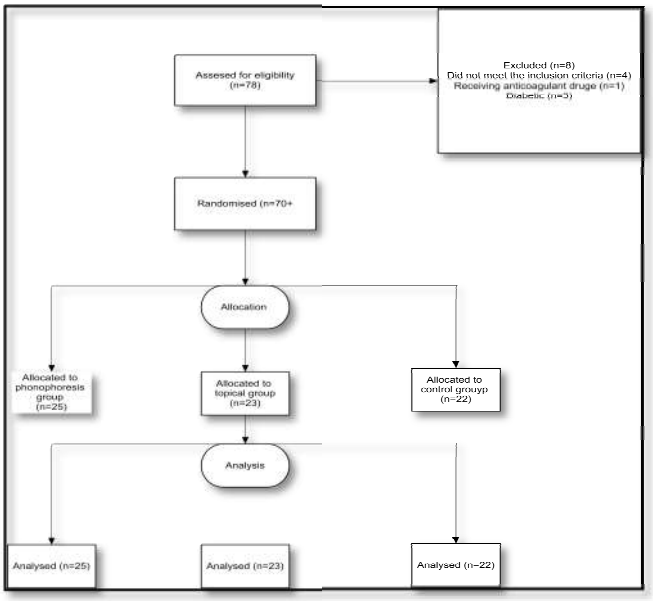

Fig 1 Flow chart of patients

Table 1 Demographic data of participates

	PH group (n=25)	Topical group (n=23)	Control group (n=22)	F-value	P value
Age (yrs.)	55.4± 6.34	55.2 ± 4.77	57±6.39	0.28	0.75 (NS)
Gender					
Female	13 (52%)	14 (60.94%)	13 (59.9%)	$\chi2$= 0.186	0.666 (NS)
Male	12 (48%)	9 (39.06%)	9 (40.1%)		
Weight (kg)	81 ± 4.83	80.8 ± 7.37	83.6±6.55	0.6	0.55 (NS)
Height (m)	167.4 ± 6.43	166.9 ± 5.7	167.7±5.07	2.04	0.95 (NS)
BMI (Kg/m^2)	28.98± 2.23	29.1 ± 2.42	29.75±2.12	0.37	0.96 (NS)

Data are expressed as mean ± SD or number (%), $\chi2$= Chi square test, NS= P> 0.05= not significant.

Table 2 illustrates the mean, SD at baseline and at the end of week 12, and % of change of VAS scores, Knee flexion ROM, and WOMAC index scores for all groups at the end of 12 weeks. It also represents the mean difference between week 12 and the baseline of all variables within groups. PH reported the highest % of increase in VAS (51.23%), knee flexion ROM (16.9%), increase in proprioceptive accuracy at 45º (61.66%) and WOMAC Index (62.7%). Topical application with Sham US reduced VAS with (25.43%), increased knee flexion ROM with (7.23%), increase in proprioceptive accuracy at 45º (32.72%) and reduced WOMAC scores with (24.73%). Control group reported the least % of decrease in VAS (3.88%), increase in knee flexion ROM (2.11%), increase in proprioceptive accuracy at 45º (3.5%) and WOMAC scores (9.5%). It also represents statistical analysis using 3x2 mixed design MANOVA indicated that there were significant overall effects of PH, Topical application and traditional physical therapy on VAS scores, active knee flexion ROM, and the WOMAC scores. For VAS (F=194.7 and P<0.0001); knee flexion ROM (F=74.53, P<0.0001), proprioceptive accuracy at 45º (F=56.6 P<0.0001) and WOMAC Index (F=124.59, P<0.0001).

There was also a significant difference between PH and topical groups regarding WOMAC scores with (P=0.039) (Table 3). The highest mean difference was between the PH and the control groups post-treatment in terms of VAS scores (1.48), active knee flexion ROM (10.99), proprioceptive accuracy at 45º (12.46) and WOMAC Index (12.46).

DISCUSSION

The current study aimed to compare between GS, CS and MSM PH and GS, CS and MSM topical application by sham US on pain, knee ROM, proprioceptive accuracy and functional disability of the knee joint in KOA. Additionally, this technique enables the clinicians to avoid prescribing per os glucosamine limiting the systemic loading**.**

Our findings were significant alleviation of pain, increased ROM, increased porprioceptive sense and decreased functional disability of the knee joint following GS, CS and MSM PH, topical application and traditional physical therapy; however PH yielded the greatest improvement of pain, ROM, position sense and function. This agrees with the results of Hedayati *et al*.

Table 2 Mean (SD) % of improvement of groups, and overall effect on VAS, ROM and WOMAC

Variable	Scores						Differences between groups	
	Baseline			Week 12 after treatment				
	PH group	Topical (Sham US) group	Control group	PH group	Topical (Sham US) Group	Control group	Overall effect	
							F-value	P-value
VAS	8.47 (0.81)	8.1 (0.87)	7.98 (1.16)	4.13 (0.95) 51.23%	6.4 (1.4) 25.43%	7.67 (1.2) 3.88%	194.7	0.0001*
Knee flex. ROM	104.04 (14.75)	104.63 (12.96)	100.27 (8.48)	121.63 (7.38) 16.9%	112.2 (7.98) 7.23%	102.39 (7.56) 2.11%	74.53	0.0001*
Prop. accuracy at 45º	5.4 (1.4)	5.5 (1.9)	5.7 (1.8)	2.07 (0.8) 61.66%	3.7 (1.4) 32.72%	5.5 (1.4) 3.5%	56.6	0.0001*
WOMAC	71.6 (13.51)	65.1 (13.69)	65.2 (8.06)	26.7 (9.93) 62.7%	49 (11.05) 24.73%	59 (8.04) 9.5%	124.95	0.0001*

Drug PH=drug (GS, CS and MSM) phonophoresis, Drug Sham-US= drug (GS, CS and MSM) sham ultrasound, Con=control group, VAS=visual analogue scale, Knee Flex.ROM=knee flexion range of motion, Prop., proprioceptive; WOMAC= The Western Ontario and McMaster Universities Osteoarthritis Index.
[a] 3 x 2 analysis of variance.
[b] Mixed-design analysis of variance F-ratio, representing interaction effect of time by group on dependent variable.
[c] Significant p-value < 0.05.
[d] Partial η2: small > 0.01, medium > 0.06, large > 0.14

Table 3 Mean difference (95% CI) and results of Boneferroni test between PH vs Topical, PH vs control, Topical vs control

Variable	Mean difference					Bonferroni test
	PH vs Topical (Sham US)	PH vs Control	Topical (Sham US) vs Control	PH vs Topical (Sham US)	PH vs Control	Topical (Sham US)vs Control
VAS	0.77 (1.57-0.34)	1.48 (2.27-0.703)	0.717 (1.51-0.78)	0.065	0.0001*	0.09
ROM	4.6 (3.19-12.41)	10.99 (3.38-18s.6)	6.38 (1.32-14.9)	0.45	0.002*	0.13
Prop. accuracy at 45º	0.88 (1.9-0.14)	1.8 (2.8-0.86)	0.98 (2.01-0.04)	0.09	0.0001*	0.06
WOMAC	8.16 (0.31-16.01)	12.46 (20.12-4.8)	4.03 (12.06-3.45)	0.039*	0.001*	0.53

*Significant at alpha level <0.05
PH, phonophoresis group; Con, control group; Sham US, Sham ultrasound.
VAS, Visual Analogue Scale; ROM, range of motion; Prop., proprioceptive; WOMAC

Between group comparison, Bonferroni correction test revealed that there was a significant difference between PH and control groups regarding VAS, active knee flexion ROM, proprioceptive accuracy at 45º and WOMAC scores (P<0.0001, P=0.002, P<0.001,P=0.001) respectively.

who found that the use of glucosamnine sulfate phonophoresis with Our results are consistent with US of continuous mode at frequency of 1 MHz and 0.3 watt/cm2 intensity, 5 min duration increasing gradually during the treatment sessions has significantly decreased pain; swelling and morning stiffness,

improved knee flexion ROM and knee function than the use of US solely with the same parameters [28]. This also consistent with the case report of Kafas *et al.* who found that Gluucosaminoglycan phonophoresis at 1 MHz and massage combined with soft mandibular splint has produced ymptomatic relief of internal derangement and muscular tension of the craniofacial system [29].

This can be attributed to the transdermal penetration induced by ultrasound [30]. Phonophersis causes significant amounts of drug are picked up by the subcutaneous circulation. Both the thermal and non-thermal characteristics of high frequency sound waves can enhance the diffusion of topically applied drugs. Ultrasound is effective in relieving pain and it causes changes in the SP threshold [31,32]. Heating from US increases the kinetic energy of the molecules in the drug and in the cell membrane, dilates points of entry such as the hair follicles and the sweat glands, and increases the circulation to the area treated with US which enhance the opportunity for drug molecules to diffuse through the stratum corneum and be collected by the capillary network in the dermis. Both the thermal and non-thermal effects of US increase cell permeability. The mechanical characteristics of the sound wave also enhance drug diffusion by oscillating the cells at high speed, changing the resting potential of the cell membrane and potentially disrupting the cell membrane of some of the cells in the area [32].

The non-thermal mechanical characteristics of ultrasound also can enhance drug diffusion by oscillating the cells at high speed, changing the resting potential of the cell membrane and potentially disrupting the cell membrane of some of the cells in the area sonicated. There may be some pushing and pulling of the cells with the propagation of the sound wave through the tissues, the effect of ultrasound on a biological system also may be associated with cavitation that is the formation of small gaseous bubbles. Cavitation may cause mechanical stress, temperature elevation, or enhanced chemical reactivity, thus affecting drug transport. The US helps more and efficient absorption of the gel which infiltrates the tissue to a higher depth than topical application [33]. Pain improvement caused by PH and topical groups may be attributed to the drug effect. MSM which is one of the basic gradients of the gel used for the treatment that evoked a number of pharmacological effects deep within the knee soft tissues, including analgesia, reducing inflammation, and inhibition of prostaglandins production [34].

Also GS and CS are the building blocks for proteoglycans and stimulate chondrocytes to make new collagen and proteoglycans. Because these supplements stimulate the production of new cartilage components that may be able to help the body repair damaged cartilage [35]. On the other hand GS serves as a precursor for, and inhibits the degradation of proteoglycans (the ground substance of articular cartilage); it rebuilds experimentally induced cartilaginous damage; and it has chondroprotective and antiarthritic effects, it has very mild anti-inflammatory and antireactive effects on edema-provoking agents including carrageenan, dextran, acetic acid and formalin [36].

Range of motion improvement in PH group might be due to pain relief and the increased tissue extensibility caused by the thermal effects of US [31,37] that allowed easier application of stretching and strengthening techniques. The increased ROM enables the patients to maintain more active knees and reduce its immobilization. The accumulated effect of stretching exercises through 12 sessions that tend to increase knee capsule extensibility and increase joint range of motion in addition to its sedative effect [38].

Improvement in the proprioception in group I may be attributed to the role of US to decrease pain, inflammation and improve functional activity and to the role of MSM induced by PH which proved to have analgesic and anti-inflammatory effect which improving the proprioceptive accuracy.

CONCLUSION

Within the limitation of this study; the use of ultrasound phonophoresis or topical application of Glucosamine sulfate, Chondroitin sulfate and Methylsulfonylmethane gel are effective and safe modalities for the treatment of knee osteoarthritis but ultrasound phonophoresis may be better for drug transportation than topical application.

Limitation

A limitation to this present study may include that no long-term follow up was preformed & we were unable to examine if our findings were actually maintained after passage of a certain period of time. Further work needs to measure the physiological responses to glucosamine sulfate, chondroitin sulfate and Methylsulfonylmethane Phonophoresis to identify the mechanisms involved. Lack of prospective trial registration is another serious limitation of the study.

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