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Original Article

Efficacy of Mesotherapy for Pain, Function and Quality of Life in Patients with Mild and Moderate Knee Osteoarthritis: A Randomized Controlled Trial

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Abstract

Objective: To investigate the effects of mesotherapy in patients with mild to moderate knee osteoarthritis (KOA). **Methods**: The study included 43 patients (56 knees) who were randomly assigned to either the mesotherapy group (MG, n=28) or the saline group (SG, n=28) and received a total of 4 weekly mesotherapy (MG) or saline injections (SG). Pain, functional status and quality of life were evaluated by a Visual Analogue Scale (VAS), the Western Ontario Universities Osteoarthritis Index (WOMAC) and the Short Form-36 (SF-36) subscales at baseline and at 8 and 16 weeks of follow-up. **Results**: A total of 39 patients (52 knees) completed the study. Eight weeks after treatment, a significant improvement was found in VAS pain scores, WOMAC scores and physical component scores (PCS) of the SF-36 in both groups compared to baseline ($p<0.05$). The VAS activity pain score, WOMAC-pain, WOMAC-physical function and WOMAC-total scores were found to have decreased significantly in the MG compared to the SG ($p<0.001$) at both 8 weeks and 16 weeks. The PCS scores significantly improved in the MG compared to the SG at 8- and 16-week follow-ups ($p<0.001$ and $p<0.001$, respectively). **Conclusions**: Mesotherapy is a well-tolerated, safe and effective alternative treatment option in patients with mild and moderate KOA.

Keywords: Functional Status, Knee Osteoarthritis, Mesotherapy, Pain, Quality of Life

Introduction

Osteoarthritis (OA) is a degenerative joint disease that significantly affects the quality of life (QoL) of patients by causing pain and functional limitation, which increases in frequency with aging, obesity and joint injuries. Although the exact pathogenesis of OA is not fully defined, the OA pathophysiology is characterized by structural changes in articular cartilage, subchondral bone, ligaments, capsule, synovial membrane and periarticular muscles[1,2]. Current guidelines recommend pharmacologic therapies, intraarticular injections, and physical, psychosocial and mind-body approaches for the management of knee osteoarthritis (KOA)[2-4]. Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used in pharmacological treatments. Although the effects of oral NSAIDs vary between different doses and drug types, they have been shown to be associated with clinically significant improvement in both pain and function in OA[1]. However, due to the gastrointestinal, renal and cardiovascular side effects of NSAIDs, their use is limited in some patients[5,6]. Therefore, the demand for alternative OA treatments is increasing.

Mesotherapy is a treatment technique consisting of a series of injections of pharmacological substances into the surface layer of the skin, first described by Dr. Michel Pistor in 1958[7]. The purpose of this treatment is to obtain direct and prolonged pharmacological effects at a local site. The slow diffusion of the drug allows low-dose drug use relative to the systemic route, as well as a synergistic effect with other pharmacological and non-pharmacological therapies. The Italian Society of Mesotherapy released a consensus report regarding the use of mesotherapy, its indications,

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contraindications and scientific evidence[8]. Although the exact mechanism of mesotherapy is unknown, several studies have shown a prolonged concentration of drugs in local tissues following intradermal injections compared to intramuscular injections[7,8]. Mrejen et al. conducted a study to determine whether there was a difference between the diffusion of products injected into the dermis at depths of 4 mm and 10 mm. Their study revealed that the product injected at a depth of 10 mm diffuses rapidly and reaches the circulatory system faster than when injected at 4 mm. Based on the aforementioned study, it has been recommended that injections not be made with a depth greater than 4 mm[9].

A systematic review by Faetani et al. reported that mesotherapy may be effective in pain relief and functional improvement in musculoskeletal pain and that it could allow patients early access to rehabilitation, leading to better QoL[10]. However, only a limited number of randomized-controlled studies have examined the effect of mesotherapy in KOA[6,11,12]. The aim of our study was to compare the efficacy of mesotherapy versus saline injections in reducing the pain and improving the function and QoL of patients with KOA.

Materials and Methods

In this prospective, randomized, single-blind, placebo-controlled study, 90 consecutive patients with KOA were recruited. A total of 43 patients (56 knees) aged 50-75 years, who attended the physical medicine and rehabilitation outpatient clinic between April 2020 and September 2020 and met the eligibility criteria, were included in the study. Inclusion criteria were a diagnosis of KOA according to clinical criteria of the American College of Rheumatology[13] that did not respond to conservative therapies such as oral or topical NSAIDs and physical therapy, with symptom duration of at least 3 months, and grade 2 or 3 (mild or moderate) KOA according to Kellgren-Lawrence classification[14]. Clinical diagnosis of KOA is made on the basis of symptoms including pain, brief morning stiffness, and functional limitations and physical examination findings such as crepitus, restricted or painful movement, joint tenderness, and bony enlargement[13].

According to the treatment algorithm published by the Italian Mesotherapy Association in 2012[8], patients with a knee activity pain Visual Analogue Scale (VAS) score of 5-7 were included. The exclusion criteria were as follows: presence of severe deformity in the lower extremity, history of surgical intervention in the lower extremity in the last 6 months, previously diagnosed rheumatologic disease, physical therapy and intra- or periarticular injection to the knee during the past 3 months, history of major trauma in the lower extremity in the previous 3 months, presence of major depression, history of drug allergies, presence of neuropathic pain, and patients on anticoagulant drugs (low molecular weight heparin, warfarin) or with bleeding disorders.

The participants were randomly assigned to the mesotherapy group (MG, n=28) or the saline group (SG, n=28), according to the order of inclusion using the computer-generated randomization method by an independent blinded researcher. The patients were blinded to the saline and mesotherapy injections. No blinding was performed for the injector or data assessors.

Interventions

Mesotherapy injection was applied using point-to-point and nappage technique with disposable sterile syringes with 30G x 4 mm needle (Meso-Relle, Biotekne, SRL, Italy). The injection contained a mix of 1 mL of 1% lidocaine (2% Jetmonal, Adeka Pharma Co., Istanbul, Turkey); 1 mL of meloxicam 3:1 diluted with saline (Melox 15 mg/1.5 ml; Nobel Pharma Co., Istanbul, Turkey), 20 mg/1 mL of pentoxifylline (Trentilin 100 mg, Santa Pharma Co., Istanbul, Turkey) and 1000 mcg/1 mL cyanocobalamine (Dodex 1000 mcg/1 mL Deva Holding Pharma Co., Istanbul, Turkey) for each session. In the mesotherapy group, point-to-point technique (injection depth of 4 mm, perpendicular to the skin) was applied to 4 points on the anterior aspect of the knee and 2 points on the posterior aspect of the knee by palpating the most painful points. Additionally, nappage technique (injection depth of 2 mm, at a 45-degree angle to the skin) was applied diagonally to the front of the knee for 5 rows around the patella. Illustrations of injection sites are presented in Figure 2. The order of drug withdrawal into the syringe was as follows: lidocaine, pentoxyfilline, cyanocobalamine and meloxicam. In the control group, in contrast to mesotherapy injections, 2 mL of saline injections were administered subcutaneously to randomly chosen points on the knee with disposable sterile syringes with 30G x 4 mm needles. Injection area was prepped with alcohol-based disinfectant. In both groups, each patient received injection treatments once a week for a total of 4 weeks.

All participants were advised only to take acetaminophen when needed and avoid using any other anti-inflammatory medication and starting new therapy including physiotherapy, and applying cold or hot-pack for their KOA during this study period. The study flow chart is shown in Figure 1.

Outcome Measures

Pain severity were evaluated using the VAS; pain, stiffness, and physical function were evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); and QoL was evaluated using the Short Form-36 (SF-36) health survey at the baseline, at 8 weeks, and at 16 weeks.

The levels of pain during activity, at rest and at night in the last 24 hours were evaluated by the VAS and scored from 0 to 10, with 0 indicating no pain and 10 the worst pain[15]. Knee-specific symptoms were asked based on the following question: "Please rate the average pain that you've had in your right/left knee in the last 24 hours during activity."

The WOMAC is the most widely used health status measurement instrument to evaluate the course of the

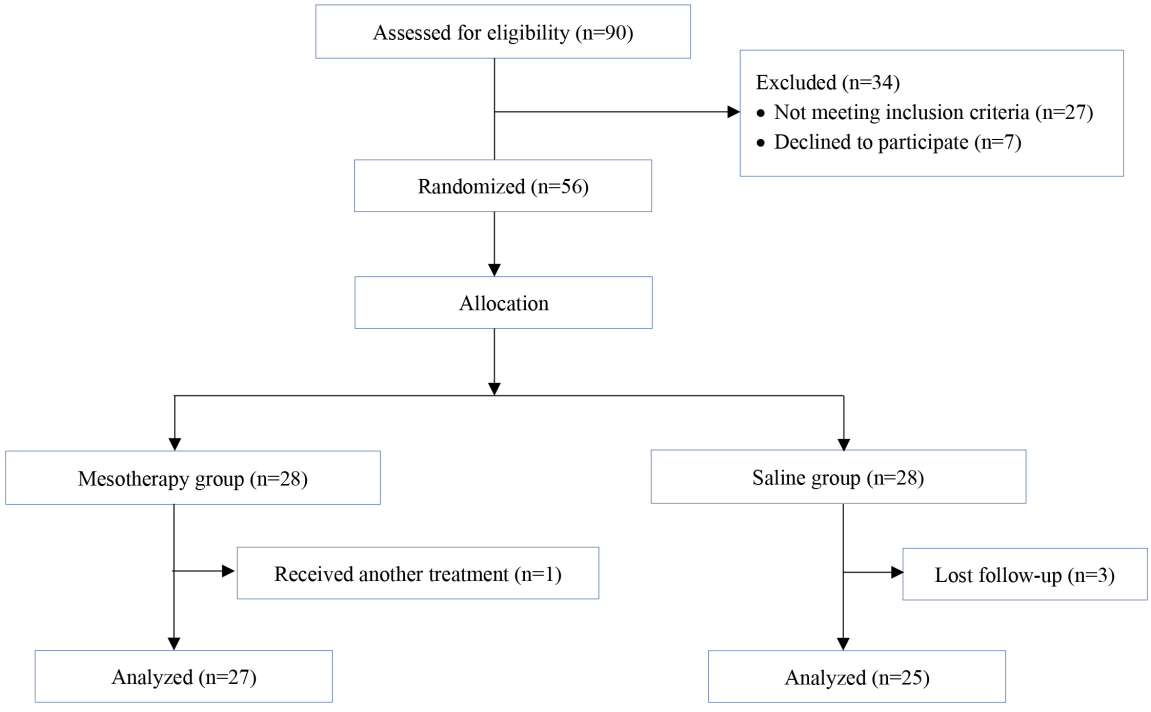

Figure 1. Flow chart.

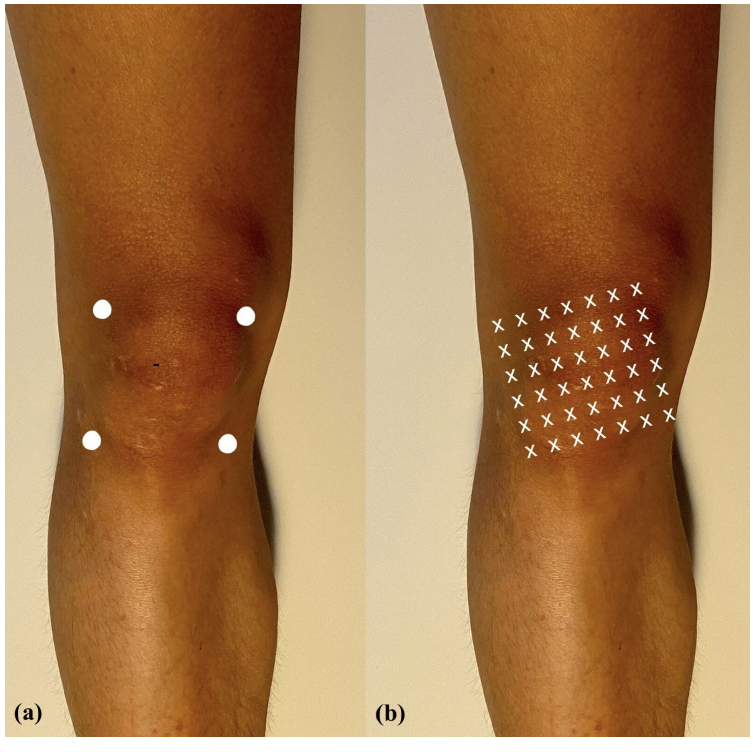

Figure 2. Injection sites used for mesotherapy. (a) anterior point-to-point technique; (b) nappage technique.

Table 1. Homogeneity of demographic and clinical variables between the two groups at baseline.

	MG (n=28)			SG (n=28)			p
	n	%	Mean ±SD	n	%	Mean ±SD	
Age (years)			59.4±6.9			61.2±7.1	0.444[a]
Body Mass Index (kg/m²)			28.4±4.9			29±4.1	0.649[a]
Duration of symptoms (months)			9.5±7.6			9.2±6.6	0.873[a]
Sex							
Women	19	90.5		14	77.8		0.273[b]
Men	2	9.5		4	22.2		
Job							
Housewife	15	71.4		12	66.7		0.284[b]
Active employee	2	9.5		0			
Retired	4	19		6	33.3		
Kellgren-Lawrence grading							
Grade 2	8	29.6		9	36		0.625[b]
Grade 3	19	70.4		16	67.3		
Location of symptoms							
Right	11	40.7		4	16		0.124[b]
Left	4	14.8		7	28		
Both	12	44.4		14	56		

[a]Independent Samples t-Test (a=0,05), [b]Chi Square (a=0,05), SD, standard deviation; MG, mesotherapy group; SG, saline group.

disease or response to treatment in patients with OA. It consists of 24 items over 3 subscales- 5 for pain, 2 for joint stiffness and 17 for physical function; each item is scored on a 5 five-point Likert scale, with higher scores indicating worse pain, more stiffness and more functional limitations[16]. The validity and reliability of the Turkish version of the WOMAC have been confirmed[17].

The SF-36 is a frequently used measurement tool to evaluate the QoL of patients with rheumatic diseases such as KOA. It evaluates a total of 8 health areas: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health[18]. The physical health subscale scores can be summarized into a physical component summary (PCS) score, while the mental health subscale scores can be summarized into a mental component summary (MCS) score[19]. These two summary components were used in the study for statistical analysis to reduce the number of statistical comparisons. The summary subscale scores range from 0 to 100, with higher scores indicating a better health status. The validity and reliability of the SF-36 have been confirmed for the Turkish population[20].

Statistical Analysis

The sample size was determined based on a statistical analysis that considered data from previous studies on injection therapy in KOA[21]. A total sample size of 25 patients in each group would be needed to have a power of 80% at a significance level of 5% to obtain the modest effect size (0.75). Due to the dropout rate of 10%, the corrected number of subjects was found to be 28 in each group. All data were analyzed using the SPSS (Statistical Package for the Social Science) software version 22.0 (IBM Corp., Armonk, NY) and are given as mean±standard deviation. The Friedman test was used for three related samples, and the Wilcoxon signed-rank test was used for two related samples, for WOMAC scores (total, pain, stiffness and physical function), VAS-activity pain, and PCS and MCS scores. Comparisons between the two groups were done using the Mann-Whitney *U* test.

Results

Of the 56 participants included in the study (Figure 1), one withdrew from the study to receive another treatment for the knee (n=1 in the MG), and three others were lost to follow-up (n=3 in the SG); these participants were not included in the statistical analysis. Thirteen patients were diagnosed with bilateral KOA and 30 patients with unilateral KOA. No significant difference was determined between the groups in terms of all demographic and clinical characteristics (Table 1).

Baseline Outcome Measures

There was a significant difference in the WOMAC-stiffness (p=0.040) and PCS scores of the SF-36 (p=0.036) at baseline between the groups (Table 2); however, no significant

Table 2. Homogeneity of outcome variables between the two groups at baseline.

	MG (n=28)	SG (n=28)	p[a]
	Mean ±SD	Mean ±SD	
Pain activity (VAS)	6.6±0.6	6.5±0.9	0.931
Pain at rest (VAS)	1.9±2.4	1.2±2.2	0.190
Pain at night (VAS)	2.1±2.5	1.9±2.4	0.791
WOMAC-pain	9±4.4	7.4±3.2	0.138
WOMAC-stiffness	3.7±2.2	2.4±2.3	0.040
WOMAC-physical function	30.5±13.8	25.6±11.3	0.212
WOMAC-total	43.2±19.5	35.4±15.6	0.138
SF-36, PCS (0-100)	32.1±7.7	36±6,6	0.036
SF-36, MCS (0-100)	46.5±8.5	48.3±8.9	0.431

[a]Mann-Whitney U test (a=0,05). MCS, mental component summary; MG, mesotherapy group; PCS, physical component summary; SG, saline group; SD, standard deviation; SF-36, short form-36; VAS, visual analogue scale; WOMAC, Western Ontario Universities Osteoarthritis Index.

differences were observed for other outcome measures (p>0.05).

The VAS activity pain and WOMAC-pain scores significantly decreased at 8 weeks (p<0.001 and p<0.001, respectively) and 16 weeks (p<0.001 and p<0.001, respectively) after the treatment in the MG compared to the SG (Table 3). The WOMAC-stiffness and WOMAC-physical function scores also decreased in the MG at 8 (p=0.001 and p<0.001, respectively) and 16 weeks (p<0.001 and p<0.001, respectively) after the treatment compared to the SG (Table 3).

The VAS rest pain scores significantly decreased in the MG at 8 (p=0.025) and 16 weeks (p=0.006) after the treatment compared to the SG, while the VAS nocturnal pain scores decreased only in the MG at 8 weeks after the treatment (p=0.043). In the SF-36 subgroup analysis, the PCS scores showed a significant increase in the MG at both 8 (p<0.001) and 16 weeks (p<0.001) after the treatment compared to the SG. However, no significant difference was found in the MCS scores of the SF-36 between the groups (Table 3).

The treatments were well tolerated by the patients. A mild, but not very disturbing burning sensation for a short period of time during the needle insertion was described by almost all the patients. Five patients (n=3, MG; n=2, SG) had bruising at the needle insertion site, which disappeared in the following days. Side effects such as allergies, dizziness and infection were not observed.

Discussion

The main finding of our study was significant pain relief obtained with the mesotherapy injections compared to the saline injections in patients with mild and moderate KOA. This positive effect can occur within 4 weeks post-injection and remain beneficial up to 3 months. Moreover, mesotherapy was effective for improving the functional status and health-related QoL. Several studies investigating the effectiveness of mesotherapy in various musculoskeletal pain conditions have reported favorable results[11,12,22-25].

The design of the studies and treatment protocols applied for mesotherapy in patients for musculoskeletal pain conditions differ. Most of the studies compared mesotherapy with oral NSAIDs; however, we evaluated the efficacy of mesotherapy compared with saline injection. A meta-analysis demonstrated that placebo injections have a significant effect on pain and function in patients with KOA[26]; therefore, in our study, saline injection was determined as the control group due to the potential placebo effects of injection therapies. Saggini et al. compared sodium diclofenac mesotherapy (1 mL of 25 mg/mL 3 times a week for 3 weeks) and oral sodium diclofenac (50 mg/day for 3 weeks) treatments in a total of 117 patients with pes anserine bursitis associated with grade-2 Kellgren Lawrence KOA[11]. The primary outcome measures were pain intensity, as assessed by VAS, and ability in daily life activities based on Knee Injury and Osteoarthritis Outcome Score, which were evaluated at baseline and at 30, 60 and 90 days after the last treatment. The authors noted that both treatments significantly reduced pain levels and disability in daily life activities, which was maintained for up to 3 months only in the mesotherapy group. In another controlled study, the efficacy of piroxicam mesotherapy and oral piroxicam treatments were evaluated in KOA[12]. One group of patients received subcutaneous piroxicam mesotherapy injections consisting of 20 mg/1 mL of piroxicam and 2 mL of 2% lidocaine 2 times at a 10-day interval to painful points around the knee (2–6 points), and the patients in the oral treatment group were prescribed 20 mg of piroxicam daily for 10 days. The authors reported that there was no significant difference between the two groups at any time on the VAS score, but that improvements in the WOMAC and the Oxford Knee Scale scores were significant in the mesotherapy group at 2, 4, and 8 weeks of follow-up[12]. In previous studies, mesotherapy injections in KOA led to

Table 3. Changes in outcome measure values between the groups from the baseline to 8-week and 16-week after the treatment.

Outcomes	Group	Mean±SD, Median (Min-Max)			8-week vs Baseline		16-week vs Baseline	
		Baseline	8-week	16-week	p#	p ‡	p#	p‡
Pain at activity VAS, (0-10)	**MG**	6.6±0.6, 7 (5-7)	3.4±1.3, 3 (0-6)	3.3±1.6, 3 (0-7)	<0.001	<0.001	<0.001	<0.001
	SG	6.5±0.8, 7 (5-7)	5.0±0.9, 5 (3-7)	6.3±0.8, 6 (5-8)	<0.001		0.265	
Pain at rest VAS, (0-10)	**MG**	1.9±2.4, 0 (0-7)	0.4±0.9, 0 (0-3)	0.4±0.8, 0 (0-3)	0.003	0.025	0.003	0.006
	SG	1.2±2.2, 0 (0-7)	0.9±1.7, 0 (0-6)	1.3±2.1, 0 (0-8)	0.203		0.756	
Pain at night VAS, (0-10)	**MG**	2.1±2.5, 2 (0-7)	0.9±1.6, 0 (0-5)	0.8±1.6, 0 (0-6)	0.001	0.043	0.003	0.066
	SG	1.9±2.4, 0 (0-7)	1.5±2.2, 0 (0-7)	1.6±2.3, 0 (0-8)	0.014		0.084	
WOMAC-Pain (0-20)	**MG**	9±4.4, 7 (3-17)	3.6±2.5, 3 (0-12)	3.3±3.6, 2 (0-16)	<0.001	<0.001	<0.001	<0.001
	SG	7.4±3.2, 6 (4-16)	5.6±3.4, 4 (2-15)	7.6±3.6, 7 (3-16)	0.001		0.597	
WOMAC-Stiffness (0-8)	**MG**	3.7±2.2, 4 (0-7)	1.2±1.5, 1 (0-5)	0.9±1.5, 0 (0-6)	<0.001	0.001	<0.001	<0.001
	SG	2.4±2.3, 2 (0-8)	1.7±1.8, 1 (0-6)	2.4±2.1, 2 (0-7)	0.018		0.713	
WOMAC-Physical function (0-68)	**MG**	30.5±13.8, 27 (7-57)	14.6±8.9, 13 (3-36)	12.9±10.9, 10 (3-48)	<0.001	<0.001	<0.001	<0.001
	SG	25.6±11.3, 25 (4-58)	20.7±8.9, 18 (3-38)	25.1±10.5, 23 (8-50)	<0.001		0.463	
WOMAC-Total (0-96)	**MG**	43.2±19.5, 40 (13-80)	19.3±12, 19 (4-52)	17.1±15.4, 13 (3-66)	<0.001	<0.001	<0.001	<0.001
	SG	35.4±15.6, 33 (9-79)	28.0±13.2, 23 (6-57)	35±15.1, 30 (12-71)	<0.001		0.499	
SF-36, PCS (0-100)	**MG**	32.1±7.7, 32 (21.5-50.7)	42.9±6.7, 43.2 (29.1-56.6)	44.2±7.1, 46 (24.1-56.2)	<0.001	<0.001	<0.001	<0.001
	SG	36.0±6.6, 37.1 (19.7-47.3)	39.4±5.6, 39 (26.8-50.9)	36.9±5.8, 37.2 (23.6-47.3)	<0.001		0.113	
SF-36, MCS (0-100)	**MG**	46.5±8.5, 48.2 (32.7-58.5)	47.8±5.6, 48.6 (34.2-57.3)	48.2±5.7, 48.9 (34.2-56.8)	0.380	0.384	0.196	0.963
	SG	48.3±8.9, 51 (27.1-58)	48.0±9.8, 50 (24.4-61.2)	48.7±9.7, 51 (26.9-63.8)	0.056		0.913	

MCS, mental component summary; MG, mesotherapy group; PCS, physical component summary; SG, saline group; SD, standard deviation; SF-36, short form-36; VAS, visual analogue scale; WOMAC, Western Ontario Universities Osteoarthritis Index. Within Group Comparison, # Wilcoxon S Rank test, (a=0,05). Between Groups Comparison, ‡Mann Whitney U test, (a=0,05).

clinically important improvements in pain intensity, which was defined as a reduction of 2 points or 30% in the pain intensity numeric rating scale (NRS)[11,12,27]. Similarly, in our study, the mean improvement in the VAS activity pain score was 3.3 points for the MG and 0.2 points for the SG at 16 weeks.

Ferrara et al.[22] conducted a retrospective study to compare the effects of mesotherapy (1 mL saline solution, 0.5 mL of 2% lidocaine hydrochloride and 0.5 mL of lysine acetylsalicylate) and saline injection in the treatment of chronic spinal pain. Patients received mesotherapy or saline injection once a week for 5 weeks and were assessed at baseline, at the end of the 5-week treatment, and at 4 weeks and 12 weeks post-treatment using VAS, the short-form McGill Pain Questionnaire and the Present Pain Intensity Scale. The aforementioned study showed that both groups experienced significant improvement in all outcome measures at the end of the 5-week treatment; however, a significant difference in the VAS pain score at 12 weeks was found only in the mesotherapy group[22]. Similarly, in the current study, improvement in the VAS pain scores of the MG continued until 12 weeks after the last treatment and significant differences were detected between the two groups.

Chen et al.[6] reported an improvement in biochemical markers and clinical conditions of patients with KOA who were treated with mesotherapy. In their study, a control group was treated with 75 mg of oral diclofenac (twice per day) for 3 months, and the patients in the mesotherapy group received two different protocols depending on the phase of KOA. Injection techniques including IDP (profound intradermic injection, injection depth=2–4 mm) and IDS (superficial intradermic injection, injection depth=1-2 mm)

were used during each session in the mesotherapy group for both protocols. The efficacy and safety of mesotherapy were evaluated with WOMAC at baseline and 6 months after treatment. The authors observed better results and lesser side effects in the mesotherapy group. In the current study, SG exhibited significant decrease in the activity pain and WOMAC scores when compared with the pre-treatment scores at 8 weeks, MG group showed significant improvements at 8 and 16 weeks when compared to the SG in terms of all outcome measures except nocturnal pain. Therefore, mesotherapy appear to be effective, compared with saline injection, in terms of improving pain and functional status in mild and moderate KOA. However, the short-term symptom relief obtained with saline injections may be related with the potential plasebo effect which demonstrated in clinical trials for KOA[28,29].

Mesotherapy was effective in improving the QoL of patients. The 33.6% improvement at 8 weeks and 37.7% improvement at 16 weeks of follow-up in the PCS exceeded the previously reported minimal clinically important difference of 12% between baseline and 3 months after treatment[30]. These results indicated that the improvement observed in the SF-36 PCS was compatible with the results obtained for the evaluation of pain and functional status. In previous studies, significant improvements were noted in the self-reported knee-specific QoL assessment based on the WOMAC[6,12]. However, in this study, QoL was evaluated in a more detailed way using the SF-36. Significant improvements were found in both groups at the 8-week follow-up, but the increase was statistically significant only in the MG for both follow-up timelines.

Other injection therapies such as platelet-rich plasma (PRP) and prolotherapy injections are commonly used in KOA. Rabago et al.[21] investigated the effects of dextrose prolotherapy in a total of 90 patients with chronic knee pain associated with KOA. The patients were randomized into three groups and followed up for 52 weeks. The first group received dextrose prolotherapy injections, the second saline injections and the third group received a home exercise program. A significant improvement was found in the mean total WOMAC score in the dextrose prolotherapy group at 52 weeks after treatment compared to the other groups. The changes in the mean total WOMAC score at 12 weeks after treatment was 13.31 points in the dextrose prolotherapy group, 8.19 points in the saline injection group and 4.26 points in the exercise group compared to the pre-treatment scores. In our study, WOMAC score changes evaluated at 12 weeks after the treatment compared to baseline were 26.1 points for the mesotherapy injection group and 0.4 points for the saline injection group. Further studies with larger samples and longer-term findings are needed to compare the effectiveness of different injection therapies in KOA.

Studies have shown that synovitis and OA progression are closely related; therefore, the inhibition of inflammation is important in the treatment of OA[31]. The role of NSAIDs in OA treatment is provided by the anti-inflammatory and analgesic effects of mesotherapy[6]. In previous studies, mesotherapy injections were administered with different ingredients and protocols, and it has been shown that different NSAIDs are effective in mesotherapy in the treatment of KOA-related pain[6,11,12]. Therefore, due to NSAIDs with their potential anti-inflammatory and analgesic effects, NSAIDs have an important contribution.

In the current study, mesotherapy were performed as 4 weekly administrations, point-to-point technique and nappage technique. In light of the results of randomized controlled studies on the efficacy of mesotherapy in musculoskeletal disorders, the mesotherapy treatment protocol used in our study was determined[8,10]. However, no consensus has yet been reached regarding how frequently the injections should be applied, or which application procedures should be preferred. Additionally, the mesotherapy treatment protocol was heterogeneous in terms of injected drugs[32]. Patients were treated with a drug mixture containing NSAID in addition to local analgesic, vasodilator, cyanocobalamine, and physiological saline solution. In the vast majority of mesotherapy protocols, either lidocaine 1% (for acute conditions) or procaine 1% (for chronic conditions) without epinephrine is used to minimize the pain of the procedure. Pentoxifylline is also commonly used and is believed to increase local tissue microcirculation, and facilitate metabolic waste elimination[33]. Cyanocobalamine is not typically used for mesotherapy in musculoskeletal disorders. However, previous studies have shown that neuropathic-like pain and pain sensitization are present in patients with KOA[34]. Therefore, the drugs used for mesotherapy in the current study might have affected our results and their variability.

Strengths and limitations of the study

The main strength of this study is its prospective and randomized-controlled design. In the literature review, no similar studies comparing the effects of mesotherapy and saline injections in KOA were found. However, a limited number of studies have compared the effectiveness of mesotherapy and oral NSAIDs with different protocols in patients with KOA[6,11,12]. Therefore, we believe that the data obtained in our study is important due to their contribution to the scientific literature and clinical practice. Another of the study's strengthens is its use of different evaluation parameters, such as physical function, joint stiffness and QoL measurements.

The main limitation of the study was that randomization was indirectly affected in patients who had bilateral knee injections. However, we aimed to maintain the patient's blindness by using same application procedures and the color of the drug solution during the application to both knees of the same patient. Riddle et al. investigated the relationship between pain intensity and function in patients with unilateral and bilateral symptomatic KOA and noted that pain intensity affected patient-based reporting tests and performance-based tests in different ways, depending on whether the knee pain was unilateral or bilateral[35]. It has

been stated that unilateral or bilateral knee pain is most associated with WOMAC scores and less with walking tests (performance-based tests). Additionally, the difference between the two groups in WOMAC-stiffness and PCS scores of the SF-36 at baseline may also have affected the results. Moreover, the efficacy of NSAIDs may be more pronounced immediately after treatment, but control evaluations were made 4 weeks after the last treatment in our study. A further point to consider is that all of the participants were advised to continue their routine daily life activities, and they were warned to avoid any physiotherapy sessions throughout the study. In addition, the participants were recommended to take only acetaminophen as needed. However, we did not report drug consumption and participation in training program during the follow-up period. Thus, potential additive or synergistic effects of these active treatments should be considered when interpreting the results of our study.

OA is a leading cause of disability, and its prevalence and burden will likely increase with progressive ageing. Thus, limited treatment options and the various comorbid conditions of this population have made the search for new therapies for KOA a priority. The results of the current study revealed that mesotherapy seems useful strategy to improve musculoskeletal symptoms and QoL in individuals with KOA. Considering the easy-to-apply, and safety of this treatment, it is believed that mesotherapy may become one of the promising methods for the treatment of KOA. According to our knowledge, this study is the first to determine the effectiveness of mesotherapy comparing with saline injections on various outcome measures in individuals with mild and moderate KOA. However, elucidating the effects of mesotherapy on through comprehensive studies would further contribute to identifying its optimal clinical use.

In conclusion, the use of mesotherapy in patients with KOA is a well-tolerated, safe and effective alternative treatment option that reduces pain and increases functionality and QoL. Our suggestions for further studies with a larger number of participants in terms of evaluating the long-term effects of the treatment are repeated mesotherapy sessions at regular intervals supported with performance-based tests as an objective result.

Authors' contributions

Narangerel Tseveendorj contributed to the conception, study design, data collection and analysis, interpretation and writing the manuscript. Dilsad Sindel contributed to the conception, study design, data collection, writing the manuscript and revision of drafts for submission. Sina Arman contributed to the data collection, data analysis and interpretation, writing the manuscript and revision of drafts for submission. Ekin Ilke Sen contributed to the conception, study design, interpretation of the data, writing of the manuscript and revision of drafts for submission. All authors read approved final version for publication and are accountable for all aspects of this work.

Ethics approval

Written informed consent was obtained from each patient. The study was performed in accordance with the Declaration of Helsinki and approved by Istanbul Medipol University Traditional and Complementary Medicine Practices Clinical Research Ethics Committee and Republic of Turkey Ministry of Health, respectively.

References

1. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet 2019;393(10182):1745-59.
2. Tuncer T, Cay FH, Altan L, Gurer G, Kacar C, Ozcakir S, et al. 2017 update of the Turkish League Against Rheumatism (TLAR) evidence-based recommendations for the management of knee osteoarthritis. Rheumatol Int 2018;38(8):1315-31.
3. Fernandes L, Hagen KB, Bijlsma JW, Andreassen O, Christensen P, Conaghan PG, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis 2013;72(7):1125-35.
4. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/ Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken) 2020;72(2):149-62.
5. Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. J Pharm Pharm Sci 2013;16(5):821-47.
6. Chen L, Li D, Zhong J, Qiu B, Wu X. Therapeutic effectiveness and safety of mesotherapy in patients with osteoarthritis of the knee. Evid Based Complement Alternat Med 2018;2018:6513049.
7. Mammucari M, Maggiori E, Russo D, Giorgio C, Ronconi G, Ferrara PE, et al. Mesotherapy: From historical notes to scientific evidence and future prospects. ScientificWorldJournal 2020;2020:3542848.
8. Mammucari M, Gatti A, Maggiori S, Sabato AF. Role of mesotherapy in musculoskeletal pain: opinions from the italian society of mesotherapy. Evid Based Complement Alternat Med 2012;2012:436959.
9. Mrejen D. Semeiologie, Pharmacocinetique et profondeur des injections en mèsothérapie. In: Bulletin 5 Des Communications Du 6e Congrès International de Mesothérapie; 1992; Bruxelas, Bélgica. Paris: Société Française de Mésothérapie; 1992:13-14.
10. Faetani L, Ghizzoni D, Ammendolia A, Costantino C. Safety and efficacy of mesotherapy in musculoskeletal disorders: A systematic review of randomized controlled trials with meta-analysis. J Rehabil Med 2021;53(4):jrm00182.
11. Saggini R, Di Stefano A, Dodaj I, Scarcello L, Bellomo RG. Pes anserine bursitis in symptomatic osteoarthritis patients: A mesotherapy treatment study. J Altern Complement Med 2015;21(8):480-4.
12. Farpour HR, Estakhri F, Zakeri M, Parvin R. Efficacy of piroxicam mesotherapy in treatment of knee osteoarthritis: A randomized clinical trial. Evid Based Complement Alternat Med 2020;2020:6940741.
13. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of

osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29(8):1039-49.
14. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis 1957;16(4):494-502.
15. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S240-52.
16. Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). Arthritis Care Res (Hoboken) 2011;63 Suppl 11(0 11):S208-28.
17. Tüzün EH, Eker L, Aytar A, Daşkapan A, Bayramoğlu M. Acceptability, reliability, validity and responsiveness of the Turkish version of WOMAC osteoarthritis index. Osteoarthritis Cartilage 2005;13(1):28-33.
18. Busija L, Pausenberger E, Haines TP, Haymes S, Buchbinder R, Osborne RH. Adult measures of general health and health-related quality of life: Medical Outcomes Study Short Form 36-Item (SF-36) and Short Form 12-Item (SF-12) Health Surveys, Nottingham Health Profile (NHP), Sickness Impact Profile (SIP), Medical Outcomes Study Short Form 6D (SF-6D), Health Utilities Index Mark 3 (HUI3), Quality of Well-Being Scale (QWB), and Assessment of Quality of Life (AQoL). Arthritis Care Res (Hoboken) 2011;63 Suppl 11: S383-S412.
19. Ware JE, Kosinski M, Keller SD. SF-36® Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute, New England Medical Center, 1994 .
20. Koçyiğit H, Aydemir Ö, Fişek G, Ölmez N, Memiş A. Validity and reliability of Turkish version of Short-form 36: A study of a patients with rheumatoid disorder. J Drug Ther 1999;12:102-6.
21. Rabago D, Patterson JJ, Mundt M, Kijowski R, Grettie J, Segal NA, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. Ann Fam Med 2013;11(3):229-37.
22. Ferrara PE, Ronconi G, Viscito R, Pascuzzo R, Rosulescu E, Ljoka C, et al. Efficacy of mesotherapy using drugs versus normal saline solution in chronic spinal pain: a retrospective study. Int J Rehabil Res 2017;40(2):171-4.
23. Costantino C, Marangio E, Coruzzi G. Mesotherapy versus systemic therapy in the treatment of acute low back pain: A randomized trial. Evid Based Complement Alternat Med 2011;2011:317183.
24. Kocak AO. Intradermal mesotherapy versus systemic therapy in the treatment of musculoskeletal pain: A prospective randomized study. Am J Emerg Med 2019;37(11):2061-65.
25. Viscito R, Ferrara PE, Ljoka C, Pascuzzo R, Maggi L, Ronconi G, et al. La mesoterapia come trattamento del dolore e della disabilità in pazienti affetti da cervicalgia in spondilartrosi [Mesotherapy as a treatment of pain and disability in patients affected by neck pain in spondylartrosis]. Ig Sanita Pubbl 2018;74(1):95-101.
26. Previtali D, Merli G, Di Laura Frattura G, Candrian C, Zaffagnini S, Filardo G. The long-lasting effects of "Placebo Injections" in knee osteoarthritis: A meta-analysis. Cartilage 2020;1947603520906597. Epub ahead of print.
27. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole MR. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94(2):149-158.
28. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis 2008;67(12):1716-23.
29. Altman RD, Devji T, Bhandari M, Fierlinger A, Niazi F, Christensen R. Clinical benefit of intra-articular saline as a comparator in clinical trials of knee osteoarthritis treatments: A systematic review and meta-analysis of randomized trials. Semin Arthritis Rheum 2016; 46(2):151-159.
30. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. Arthritis Rheum 2001;45(4):384-91.
31. Wei Y, Bai L. Recent advances in the understanding of molecular mechanisms of cartilage degeneration, synovitis and subchondral bone changes in osteoarthritis. Connect Tissue Res 2016;57(4):245-61.
32. Paolucci T, Bellomo RG, Centra MA, Giannandrea N, Pezzi L, Saggini R. Mesotherapy in the treatment of musculoskeletal pain in rehabilitation: the state of the art. J Pain Res 2019;12:2391-2401.
33. Sivagnanam G. Mesotherapy - The french connection. J Pharmacol Pharmacother 2010;1(1):4-8.
34. Zolio L, Lim KY, McKenzie JE, Yan MK, Estee M, Hussain SM, et al. Systematic review and meta-analysis of the prevalence of neuropathic-like pain and/or pain sensitization in people with knee and hip osteoarthritis. Osteoarthritis Cartilage 2021;29(8):1096-1116.
35. Riddle DL, Stratford PW. Unilateral vs bilateral symptomatic knee osteoarthritis: associations between pain intensity and function. Rheumatology (Oxford) 2013;52(12):2229-37.