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Research

Cost-Effective and Safe Management of Knee Osteoarthritis: Evaluating the Rapid Therapeutic Benefits of Mesotherapy

Dr. Parissa Hajizadeh*

Department of Orthopaedics, Kumaran Medical Center Hospital, DR MGR medical health University of Chennai, in state of Tamil Nadu, India

*Author for Correspondence: Dr. Parissa Hajizadeh
Email: parisahajizadeh1882@gmail.com

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Abstract

This study aimed to assess the therapeutic efficacy of mesotherapy in comparison to oral NSAIDs for the management of knee osteoarthritis (OA). Through a controlled clinical investigation, we sought to generate robust evidence on the effectiveness, safety profile, and potential of mesotherapy as an alternative treatment strategy for OA. A total of 60 Indian patients diagnosed with knee osteoarthritis were enrolled in the study and stratified into two groups based on the presence or absence of contraindications to nonsteroidal anti-inflammatory drugs (NSAIDs). Patients in Group A received standard oral NSAID therapy, while those in Group B underwent mesotherapy. All interventions were conducted under clinical supervision. Upon completion of the treatment protocol, all patients were monitored over a six-month follow-up period. A total of 50 patients successfully completed both the treatment and follow-up periods. Patients in Group B (mesotherapy) reported significantly fewer gastric acid-related complaints and required less supplementary treatment for recurrent pain compared to those in Group A (NSAIDs) ($p < 0.05$). However, mesotherapy resulted in a more substantial enhancement in physical function ($p < 0.05$). Moreover, patients in Group B exhibited superior overall outcomes compared to those in Group A, with statistically significant differences observed ($p < 0.05$ or $p < 0.01$). Our findings indicate that while both NSAID therapy and mesotherapy significantly improve biochemical markers and clinical symptoms in knee OA patients, mesotherapy is associated with fewer adverse gastrointestinal effects and a reduced need for additional pain management interventions. Our findings suggest that mesotherapy is a safe, effective, and well-tolerated treatment option for patients with knee osteoarthritis. In direct comparison with conventional NSAID therapy, mesotherapy resulted in significant improvements in pain relief and functional capacity, while also notably reducing gastrointestinal adverse effects.

Keywords: Knee Osteoarthritis, Osteoarthritis Management, Mesotherapy, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), Pain Management, Intra-articular Therapy.

INTRODUCTION

Osteoarthritis (OA) is one of the most prevalent degenerative diseases of the musculoskeletal system, significantly affecting the quality of life of individuals. In India, the prevalence of symptomatic knee OA is estimated to be 15.5% among women and 5.6% among men reported in the Osteoarthritis Study."[1] The global burden of OA is substantial, not only due to its high prevalence but also because of its economic implications. March and Bachmeier [2] reported that annual healthcare costs associated with musculoskeletal disorders range from 1% to 2.5% of the gross national product in countries such as the USA, UK, France, Canada, and Australia.

Pathophysiologically, OA is characterized by cartilage degeneration, impaired tissue repair mechanisms, and bone remodeling, often accompanied by synovial inflammation [3]. Clinically, OA leads to chronic pain, functional impairment, and stiffness, ultimately reducing mobility and independence in affected individuals. The primary goal of OA management is to alleviate pain, improve joint function, and enhance overall quality of life while minimizing medication-related adverse effects [4].

Traditionally, acetaminophen (paracetamol) has been the first-line treatment for mild knee OA. However, for moderate to severe cases, its efficacy is often inferior to that of nonsteroidal anti-inflammatory drugs (NSAIDs) [5]. A study by Arcangeli et al. demonstrated that the use of diclofenac sodium at a dose of 150 mg per day in a prolonged-release form effectively reduced pain and improved joint function in patients with osteoarthritis [6]. Despite their effectiveness, NSAIDs pose significant risks, including gastrointestinal bleeding, cardiovascular complications, and renal impairment, which limit their long-term use, particularly in elderly patients or those with comorbidities.

Given these challenges, mesotherapy has emerged as a promising alternative for localized pain management. This technique involves the intra- or subcutaneous injection of active compounds, allowing for localized and prolonged pharmacological effects while minimizing systemic side effects [7].By using lower drug doses and targeting specific areas, mesotherapy significantly reduces the risks associated with traditional systemic therapies. A 2011 expert panel reached a consensus on the scientific rationale, indications, and benefits of mesotherapy, highlighting its potential as a minimally invasive and well-tolerated treatment option [8].Previous studies have demonstrated that mesotherapy with local anesthetics, NSAIDs, muscle relaxants, and other analgesics can lead to at least a 50% reduction in pain in conditions such as cervical pain, back pain, and tendinopathies [9,10]. However, a gap remains in the literature regarding its efficacy in knee OA compared to standard oral NSAID therapy. Furthermore, the additional benefits of mesotherapy, beyond reduced side effects, are yet to be fully explored. This controlled study aims to contribute to the growing body of evidence supporting the clinical application of mesotherapy for knee OA management.

2. MATERIALS AND METHODS

2.1. Patients

Between May 2021 and June 2022, a total of 60 patients diagnosed with osteoarthritis (OA) of the knee were recruited and treated at the Department of Orthopaedics of Kumaran Medical Center Hospital of Dr. M.G.R. Medical University. The diagnostic criteria for knee OA, as established by Altman et al. [11], were used:

(1) Knee pain with at least 5 of the following characteristics: age > 50 years, stiffness lasting <30 minutes, crepitus, bony tenderness, bony enlargement, no palpable warmth, erythrocyte sedimentation rate (ESR) <40 mm/hour, rheumatoid factor (RF) <1:40, and synovial fluid analysis consistent with OA.

(2) Knee pain with radiographic osteophytes and either age > 50 years, stiffness <30 minutes, or crepitus.

Patients were randomized into two groups. Group A included 30 patients without known contraindications to NSAIDs, while Group B included 30 patients who received mesotherapy. During the study, 6 patients were excluded—3 from Group A due to gastrointestinal intolerance and 3 from Group B due to loss to follow-up-resulting in 50 patients who completed the study.

Patients with known hypersensitivity to the treatment components, those who had received corticosteroid injections, physical therapy within 5 weeks before the study, or any surgical intervention within 3 months before the study were excluded. Clinical characteristics and laboratory parameters were collected at baseline and after treatment. All patients were followed for a period of 6 months and provided written informed consent before participating.

2.2. NSAIDs

In Group A, patients received oral diclofenac (75 mg) twice daily for the first three months, followed by as-needed use based on symptom severity. To manage potential gastrointestinal side effects, patients were permitted to take misoprostol or proton pump inhibitors (PPIs) in case of dyspepsia, heartburn, nausea, or bloating. Participants were withdrawn from the study if they exhibited any signs of gastrointestinal bleeding (e.g., hematemesis, melena, or positive fecal occult blood test).

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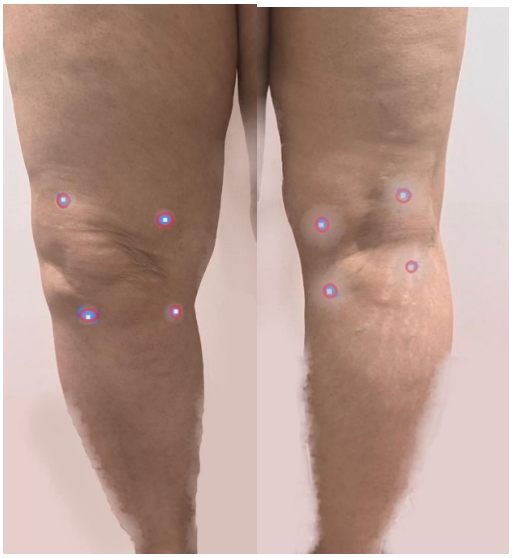

Fig 1: Injection sites used for mesotherapy. IDP (profound intradermic injection) was administered at Eight points along the joint space (four anterior and four posterior), while IDS (superficial intradermic injection) was applied to four regions of the knee.

2.3. Mesotherapy Treatment Protocol

Patients in Group B were strictly prohibited from using oral analgesics or corticosteroids during the study period. Mesotherapy was performed using disposable sterile syringes (BD), single-use sterile needles (0.26 mm × 4 mm and 0.3 mm × 13 mm, Terumo), a disinfectant, and other necessary medical supplies. Two distinct mesotherapy protocols were employed based on the patient's disease phase:

1. Acute Phase Protocol

A mixture of 2 mL of 1% lidocaine, 40 mg of piroxicam (2 mL), and 100 IU of calcitonin (1 mL) was administered. Sessions were scheduled on Day 1 (D1), Day 8 (D8), and Day 15 (D15), with additional sessions provided as needed. The total injectable volume of 5 mL was distributed across 8 injection sites around the affected knee joint, with each site receiving approximately 0.6 mL of the solution. The injections were performed using both superficial (IDS; 1–2 mm depth) and profound (IDP; 2–4 mm depth) techniques, ensuring optimal drug delivery and therapeutic effects. The goal of the acute phase protocol was to provide immediate relief from pain and inflammation.

2. Chronic Phase Protocol

A combination of 2 mL of 2% procaine, 2 mL of organic silica (Conjonctyl), and 100 IU of calcitonin (1 mL) was used. Sessions were conducted on Day 1 (D1), Day 15 (D15), Day 30 (D30), and Day 60 (D60), with supplementary sessions available upon request. Similar to the acute phase, the total injectable volume (5 mL) was distributed across multiple injection sites on the affected knee joint. The injections were performed at both superficial and profound depths to ensure effective tissue penetration and therapeutic benefit. The chronic phase protocol focused on providing long-term pain management and improving joint function.

Each treatment protocol was formulated by two certified mesotherapists and administered by the same physician throughout the study to maintain consistency in delivery.

2.4. Evaluations

The therapeutic efficacy and safety of the two treatments were evaluated for each patient at the end of the 6-month follow-up (M6) with comparisons with baseline findings (M0). The major therapeutic outcome was measured using the Indian Tamil Nadu State and DR MGR Universities Osteoarthritis Index, which includes:

- **Pain** (5 items; score range: 0–20)
- **Stiffness** (2 items; score range: 0–8)
- **Functional Limitation** (17 items; score range: 0–68)

To assess safety, all adverse events and side effects-including allergic reactions, dyspepsia, heartburn, nausea, bloating, and melena-were recorded throughout the study. In addition, laboratory parameters were measured at M0 and M6 to further evaluate both therapeutic efficacy and treatment safety.

Data source: Evidence-Based Complementary and Alternative Medicine

Table 1: Clinical Characteristics of the Included Patients

Parameter	Group A (NSAIDs)	Group B (Mesotherapy)	Statistical Significance
Gender			
Male	3	4	
Female	21	22	
Age (years)	57.2 ± 3.4	61.4 ± 6.8	
Course of Disease (years)	6 ± 4.6	9 ± 7.1	
Inflammation			
Acute Phase	17	10	
Chronic Phase	7	16	
Body Mass Inde	25.3 ± 3.6	24.7 ± 4.8	
PPIs Use (§)	5 (20.8%)	0	$p < 0.05$
Supplementary Treatment (§§)	14 (58.3%)	4 (15.4%)	$p < 0.01$

Laboratory Tests and Statistical Analysis

Parameter	Group A (Baseline)	Group A (Post-Treatment)	Group B (Baseline)	Group B (Post-Treatment)	Statistical Significance
CRP	16.62 ± 6.01	10.25 ± 3.50	16.43 ± 5.73	9.50 ± 3.46	$p < 0.05$ (Group A vs. Group B)
ESR	42.64 ± 11.77	29.31 ± 8.14	42.34 ± 10.68	21.77 ± 6.42	$p < 0.05$ (Group A vs. Group B)

Abbreviations

- BMI: Body Mass Index (kg/m²)
- PPIs: Proton Pump Inhibitors
- Supplementary Treatment: Defined as the need for additional oral NSAIDs after three months in Group A or an extra mesotherapy session in Group B.

2.5. Statistical Analysis

All statistical analyses were conducted using SPSS 22.0 software (IBM, Armonk, NY, USA). Categorical variables were expressed as frequencies (n) and percentages (%), while continuous variables were reported as mean ± standard deviation (M ± SD). Independent t-tests were used to compare continuous variables, and chi-square tests were applied for categorical variables. A p-value of <0.05 was considered statistically significant.

3. RESULTS

3.1. Patients' Clinical Characteristics

Six patients from Group A were excluded from the study due to various reasons: two were lost to follow-up, two received corticosteroid injections, one developed melena, and one experienced pruritus (itchy skin). In Group B, a total of 26 patients completed the study, with four patients lost to follow-up.

A comparison of baseline and post-treatment clinical characteristics is summarized in Table 1. Patients in Group B reported significantly fewer gastrointestinal complaints related to gastric acid ($p < 0.05$) and required less supplementary treatment for recurrent pain compared to those in Group A ($p < 0.05$). p-value "The mean VAS score was significantly reduced in both groups (Group A: from 6.8 ± 1.2 to 4.3 ± 1.0, $p < 0.01$; Group B: from 6.9 ± 1.3 to 3.1 ± 0.9, $p < 0.001$)."

3.2. Haemorheology

Dynamic changes in haemorheological parameters are outlined in Table 2. Both NSAID therapy and mesotherapy significantly reduced blood viscosity ($p < 0.05$); however, neither treatment produced significant alterations in other haemorheological parameters.

A notable decrease in erythrocyte aggregation index was observed only in Group A ($p < 0.05$), suggesting that NSAID therapy influenced this parameter. However, no significant differences were found between Group A and Group B in other haemorheological factors.

3.3. Outcome

As illustrated in Figure 2, both treatment groups experienced a significant reduction in pain scores post-treatment ($p < 0.05$ or $p < 0.01$). Additionally, patients in the mesotherapy group demonstrated marked improvement in physical function ($p < 0.05$). Notably, mesotherapy yielded greater therapeutic benefits compared to NSAID therapy, with statistically significant differences in clinical outcomes favoring Group B ($p < 0.05$ or $p < 0.01$).

3.4. Subgroups Analysis

To minimize the potential influence of inflammation, four subgroups were established for comparative analysis. Results indicated that inflammation status was an independent variable affecting haemorheological changes (Table 2).

- Acute-phase patients in Group A vs. Group B: significant differences in blood viscosity and erythrocyte aggregation index ($p < 0.05$).
- Chronic-phase patients in Group A vs. Group B: no significant differences ($p > 0.05$). Inflammation status did not significantly influence evaluations based on the Dr MGR universities osteoartitites index.

Notable improvements in treatment outcomes were observed in both acute and chronic-phase patients, as indicated by the following results:

- Acute phase (Group A vs. Group B): $p < 0.05$
- Chronic phase (Group A vs. Group B): $p < 0.05$

5. DISCUSSIONS

In this study, we evaluated the effectiveness and safety of mesotherapy as a treatment for knee osteoarthritis (OA) by comparing it with traditional NSAID therapy. Our findings indicate that both treatments significantly improved patients' biochemical markers and clinical symptoms. However, mesotherapy demonstrated superior outcomes in certain aspects, including fewer side effects, improved haemorheological parameters, and better MGR OA index scores.

5.1. Mechanisms Underlying Treatment Efficacy

Cartilage degeneration is a hallmark pathological feature of osteoarthritis (OA), with synovial inflammation playing a pivotal role in disease progression. Synovitis leads to joint swelling and pain, and considerable evidence suggests a strong association between synovial inflammation and the advancement of OA. Consequently, targeting inflammation is a fundamental objective in OA management.

Inflammatory biomarkers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are routinely utilized to evaluate disease severity and monitor therapeutic response. In this study, both NSAID therapy and mesotherapy resulted in significant reductions in blood viscosity ($p < 0.05$), potentially reflecting improvements in microcirculation within the affected joint. Enhanced blood flow to synovial tissue may facilitate better nutrient supply and further mitigate inflammation, thereby reinforcing the therapeutic efficacy of these treatment modalities.

5.2. Comparing Mesotherapy and NSAID Therapy

NSAIDs have long been considered a first-line treatment for OA due to their well-documented anti-inflammatory and analgesic properties. However, prolonged NSAID use is associated with significant adverse effects, particularly gastrointestinal complications such as gastritis, ulcers, and gastrointestinal bleeding. In contrast, mesotherapy offers a localized drug delivery system that minimizes systemic side effects while preserving potent anti-inflammatory actions. In our study, patients treated with mesotherapy required significantly fewer additional pain management interventions ($p < 0.05$) and experienced fewer gastrointestinal complaints compared to those receiving NSAIDs. These findings align with previous research, such as the randomized trial by Costantino et al. (2011) [12], which demonstrated that mesotherapy is as effective as systemic NSAID therapy in managing acute low back pain—with a lower incidence of adverse effects. Additionally, the opinions from the Italian Society of Mesotherapy further support the efficacy of mesotherapy in managing musculoskeletal pain [13]. Additionally, the significant improvements in WOMAC scores observed in the mesotherapy group suggest that this treatment provides comparable, if not superior, functional benefits for OA patients. This outcome is likely due to enhanced pain relief and improved joint mobility.

5.3. Clinical Implications and Future Directions

Given its efficacy and safety profile, mesotherapy presents a viable alternative for patients who cannot tolerate NSAIDs or for those at high risk of gastrointestinal complications. While our study provides strong evidence supporting mesotherapy's clinical benefits, further long-term, large-scale studies are necessary to:

- Optimize mesotherapy protocols for different OA severity levels.

- Compare mesotherapy with other non-pharmacological interventions such as physiotherapy or intra-articular injections.
- Assess cost-effectiveness to determine its feasibility as a routine OA treatment option.

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The following table presents the dynamic hemorheological changes observed in Groups A and B before and after treatment, including key parameters such as blood viscosity, plasma viscosity, hematocrit, fibrinogen levels, platelet sticky rate, and erythrocyte aggregation index.

Table 2: Dynamic Hemorheological Changes Before and After Treatment

Parameter	Group A (Pre-Treatment)	Group A (Post-Treatment)	p-value	Group B (Pre-Treatment)	Group B (Post-Treatment)	p-value	Group A vs. Group B (p)
Blood viscosity	5.6 ± 1.3	4.9 ± 1.4	< 0.05	5.4 ± 1.6	4.2 ± 1.8	< 0.05	> 0.05
Plasma viscosity	1.5 ± 0.4	1.4 ± 0.6	--------	1.6 ± 0.1	1.4 ± 0.2	---------	----------
Hematocrit (%)	43.7 ± 2.2	42.1 ± 2.4	—	42.3 ± 4.1	40.1 ± 2.4	---------	----------
Fibrinogen (g/L)	4.3 ± 0.9	4.0 ± 1.0	---------	4.7 ± 1.3	3.5±1.4	---------	----------
Platelet sticky rate (%)	50.0 ± 10.1	48.5 ± 3.6	> 0.05	51.4 ± 13.1	33.6 ± 4.3	< 0.05	
Erythrocyte aggregation index	9.2 ± 4.8	8.1 ± 4.7	< 0.01	9.5 ± 3.6	8.1 ± 4.2	---------	----------

• *Acute Phase: $p < 0.05$;* • *Chronic Phase: $p > 0.05$*

The results indicate a statistically significant improvement in hemorheological parameters post-treatment in both groups, with greater reductions in Group B. However, the intergroup comparison shows no significant difference between Group A and Group B ($p > 0.05$).

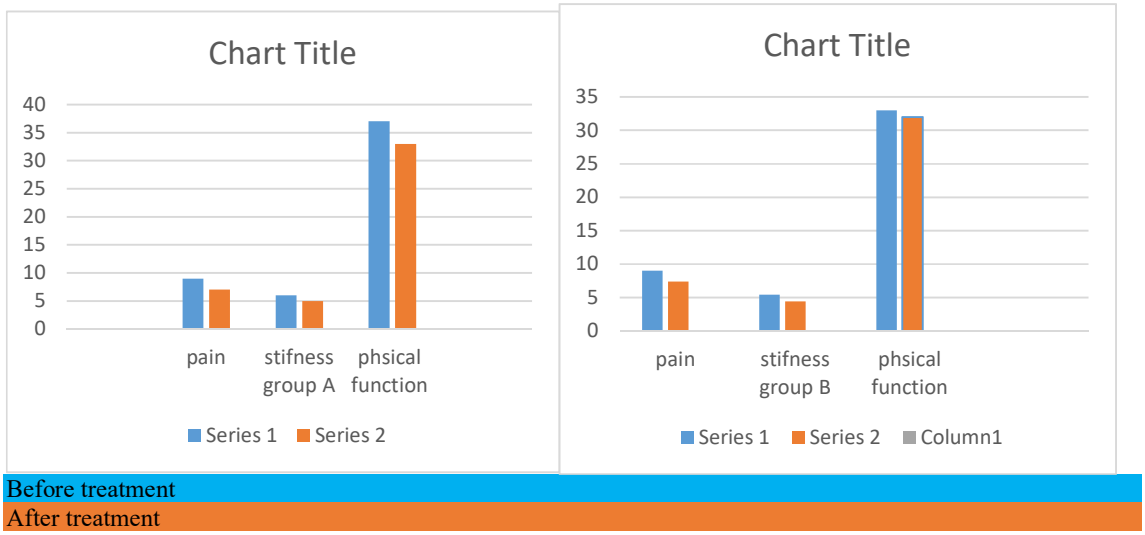

Fig 2: Clinical Outcome Evaluations – Dr. M.G.R. Educational and Research , India

The Dr. M.G.R. Educational and Research Institute Osteoarthritis Index was used to assess the clinical outcomes of patients in this study. This index includes:

- Pain: 5 items (score range: 0–20)
- Stiffness: 2 items (score range: 0–8)
- Functional limitation: 17 items (score range: 0–68)

Statistical significance

- $p < 0.05$ (*significant difference)
- $p < 0.01$ (**highly significant difference)

Pathophysiology of Osteoarthritis and Therapeutic Implications

Cartilage degeneration is a key pathological feature of osteoarthritis (OA), with synovial inflammation playing a central role in disease progression. Synovial inflammation contributes to joint swelling and pain, highlighting the close relationship between synovitis and OA progression. Consequently, targeting the inflammatory response is crucial in OA treatment [14].

Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are well-established indicators of inflammation severity and disease activity. These biomarkers serve as reliable metrics for evaluating the clinical efficacy of anti-arthritis therapies [15].

Hemorheological Changes and Treatment Efficacy

OA progression has been associated with increased blood viscosity, which impairs blood flow to the affected joints. Both nonsteroidal anti-inflammatory drugs (NSAIDs) and mesotherapy have demonstrated efficacy in reducing blood viscosity, thereby potentially enhancing circulation in the affected regions. This hemodynamic improvement supports the effectiveness of these treatments [16].

Comparative Analysis of NSAIDs and Mesotherapy

NSAIDs have long been the first-line therapy for arthritis due to their anti-inflammatory and analgesic properties. However, our findings suggest that while both NSAIDs and mesotherapy exhibit comparable therapeutic efficacy, mesotherapy demonstrated superior clinical outcomes in certain aspects. Similar trends have been reported in previous studies involving patients with pes anserine bursitis and acute low back pain [17, 18].

The observed differences between these two treatment modalities may be attributed to variations in mechanisms of action, drug delivery methods, or localized therapeutic effects. Further research is warranted to elucidate these mechanisms and optimize treatment strategies for OA management.

Evidence-Based Complementary and Alternative Medicine – Dr. M.G.R. Educational and Research Institute, India

The effectiveness of mesotherapy as an alternative treatment for osteoarthritis (OA) remains a subject of investigation. Although detection methods for mesotherapy's pharmacokinetics are limited, it is hypothesized that this technique enhances subcutaneous drug concentrations and delays systemic drug absorption . Additionally, locally injected agents appear to provide longer-lasting analgesic effects compared to systemic NSAIDs alone. For example, lidocaine administered via local injection has demonstrated prolonged analgesic activity beyond what is typically seen with oral NSAIDs [19].

One of the major challenges with NSAID therapy is the recurrence of pain upon withdrawal. Our study found that a significant number of patients who were treated with NSAIDs requested repeated treatment sessions due to recurrent pain, even after three months of continuous systemic therapy. In contrast, only a minimal number of patients in the mesotherapy group required additional treatment, suggesting greater pain relief and sustained effects with mesotherapy.

Furthermore, systemic NSAID therapy was associated with a higher incidence of adverse effects, and in some cases, patients had to withdraw from the study due to severe side effects. Given that osteoarthritis primarily affects elderly populations, the risk of NSAID-related side effects is a major concern [20, 21]. Mesotherapy, on the other hand, offers a safer alternative with localized therapeutic effects that minimize systemic complications.

Limitations of the Study

One limitation of this study is the lack of available techniques for measuring intracutaneous drug concentrations following mesotherapy administration. Consequently, the effective dosages of NSAIDs used in systemic therapy and mesotherapy cannot be directly compared due to differences in drug delivery mechanisms.

Moreover, mesotherapy is not solely a method of drug administration but also functions as a form of reflexotherapy. Research has shown that acupuncture—which shares some physiological principles with mesotherapy—can improve physical function and provide significant pain relief in patients with OA [22, 23]. To further explore this aspect, a future expanded clinical trial incorporating acupuncture therapy has been planned.

Overall, mesotherapy was well-tolerated, with minimal adverse effects, making it a promising alternative for pain management in osteoarthritis. However, before administering mesotherapy, informed consent from patients is essential [24].

5. CONCLUSIONS

Our findings indicate that mesotherapy is an effective and well-tolerated treatment option for patients with osteoarthritis (OA). Compared to systemic NSAID therapy, mesotherapy provided comparable pain relief, improved functional outcomes, and demonstrated a lower incidence of adverse effects. The localized drug delivery mechanism associated with mesotherapy appears to contribute to longer-lasting analgesic effects while minimizing gastrointestinal complications, making it a particularly suitable alternative for patients with NSAID contraindications. Despite these promising results, certain limitations must be considered. The lack of available methods for measuring intracutaneous drug concentrations following mesotherapy administration presents a challenge in directly comparing effective dosages between treatment modalities. Moreover, mesotherapy may exert therapeutic benefits beyond its pharmacological effects, potentially acting as a form of reflexotherapy, similar to acupuncture. Future research should focus on expanding patient recruitment, integrating acupuncture as a comparative intervention, and further investigating the long-term efficacy and underlying mechanisms of mesotherapy. This study was conducted at Dr. M.G.R. Educational and Research Institute, Chennai, India, and contributes to the growing body of research within the Indian medical and pharmaceutical community. Given the rising prevalence of OA in aging populations, clinicians in **India** and globally should consider mesotherapy as a viable alternative treatment, particularly for patients at high risk of NSAID-related complications.

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