Original Article

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The Clinical Effectiveness of Mesotherapy in Refractory Chronic Migraine

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Abstract

Aim: This study aimed to evaluate the clinical effectiveness of mesotherapy in patients with refractory chronic migraine (CM). The goal was to determine its impact on pain frequency, duration, and intensity and on analgesic use, thereby informing alternative therapeutic strategies for this population.

Methods: This retrospective cohort study included 27 patients diagnosed with CM. These patients received mesotherapy injections containing 2 mL of 1% lidocaine, 40 mg of piroxicam in 2 mL, and 100 U of calcitonin in 1 mL at specific anatomical sites, including the glabella, supraorbital notch, infraorbital foramen, preauricular, postauricular, and temporal masseter, fronto-occipital, and trapezius muscle trigger points. Assessment parameters included the frequency of painful days per month (PDs), the number of analgesics per month (NoA), the duration of attacks per month (DoA), and the patients' visual analogue scale (VAS) scores. Evaluations were conducted before treatment and at 4, 8, and 12 weeks post-treatment.

Results: Significant improvements were observed in the NoA, DoA, PD, and VAS scores at 4 and 8 weeks post-treatment, compared with pre-treatment values. Although efficacy declined by week 12, scores remained higher than baseline. No adverse events were reported.

Conclusion: Mesotherapy appears to be an effective treatment for CM, with notable improvements in pain frequency, duration, and severity and a reduced need for analgesics over 12 weeks. To more thoroughly assess this efficacy, large-scale, prospective, randomized controlled studies are required.

Keywords: Pain, migraine disorders, mesotherapy, piroxicam, analgesics

Introduction

Headache is a common neurological symptom with a multifactorial etiology and represents one of the most frequent causes of outpatient visits worldwide. Common causes of headache include migraine, tension-type headache, and cervicogenic headache (1). Migraine is a condition characterized by recurrent headaches often accompanied by sensory, emotional, and cognitive symptoms, particularly affecting the productivity of the younger population aged 15-49 (1,2). The International Headache Society defines chronic migraine (CM) as a headache persisting for more than three months without excessive medication use, occurring on at least 15 days per month, with episodes lasting 4-72 hours, including at least eight days with migraine features. Accompanying symptoms may include nausea, vomiting, visual disturbances, and sensitivity to light, sound, and odors (1,3).

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Chronic migraine is treated with a combination of pharmacological and non-pharmacological approaches to alleviate pain and reduce the frequency, duration, and intensity of attacks (1,4). Mesotherapy is an intradermal technique that involves injecting a specialized mixture into the superficial dermis using microneedles. Modern mesotherapy approaches advocate administering a solution in minimal quantities (5). Mesotherapy is thought to be effective in pain management by boosting endorphin levels, eliciting reflex responses to needle stimulation, and inducing local effects through the gradual diffusion of the medications (5,6). Mesotherapy can be deemed an effective treatment approach for headaches, lower back and neck pain, fibromyalgia, and musculoskeletal pain (5,7,8).

We hypothesized that mesotherapy, an intradermal injection technique using low-dose medication mixtures, could provide clinical benefit in refractory CM. There is a notable gap in the literature regarding studies demonstrating the effectiveness of mesotherapy in the treatment of CM. This study aims to assess the efficacy of mesotherapy in the management of CM.

Materials and Methods

Compliance with Ethical Standards

The principles of the Declaration of Helsinki were followed during this study. Ethical approval was obtained from the University of Health Sciences Türkiye, Kanuni Sultan Suleyman Training and Research Hospital Ethics Committee (approval no.: KAEK/2022.11.225, date: 21.11.2022). Informed consent for publication was obtained from the patients after they agreed that their anonymized case data could be summarized and analyzed. The signed documents are confidential.

Study Population

This retrospective interventional cohort study enrolled 27 patients diagnosed with CM who were referred to and treated at our integrative medicine and rehabilitation clinic between January 2019 and June 2022, and data extraction, analysis, and manuscript preparation were completed between January 2023 and December 2024. All participants met the criteria for refractory CM as outlined by the European Headache Federation (9). All patients had undergone at least one year of preventive therapy for CM prior to participating in the study. Signed informed consent was obtained from each participant.

Before mesotherapy, all patients underwent routine blood tests, including a complete blood count, thyroid function tests, liver function tests, kidney function tests, blood glucose measurement, and screening for markers of viral infections, including human immunodeficiency virus, Hepatitis B, and Hepatitis C. Patients were included in the study after the exclusion of infections, thyroid dysfunction, anemia, and systemic illnesses. Chronic illnesses and allergies were documented for each patient.

Patients were regularly monitored at 4-week intervals over a 12-week period to assess treatment effectiveness. The evaluation included the frequency of painful days per month (PD), the number of analgesics taken per month (NoA), the duration of attacks per month (DoA), and patients' visual analogue scale (VAS) scores, measured before treatment (baseline measurement) and at 4, 8, and 12 weeks post-treatment. Additionally, the use of analgesics (including ergot alkaloids, triptans, and others) was quantified as the number of doses per month.

None of the patients had contraindications to injections, including conditions such as malignant hypertension, medication overuse, intracranial pathologies such as open skull defects, known allergies to anesthetic agents or piroxicam, systemic or local infections, anticoagulant use, or a tendency toward vasovagal responses to injections.

The study flowchart is shown in Figure 1.

Mesotherapy Treatment Protocol

Mesotherapy employs various injection techniques to deliver drug mixtures precisely to the intended anatomical site. These injections can be administered via syringes, mechanical or electronic injection devices, or pneumatically powered portable injection guns. In this study, 10 mL syringes were used. Injections were performed at 21 predefined sites (glabella, supraorbital notch, infraorbital foramen, fronto-occipital, preauricular and postauricular zones, temporal trigger points, and masseter and trapezius muscles). Figures 2 and 3 show schematic illustrations of the anatomical sites for mesotherapy application and of the standardized injection, respectively.

Figure 2 legend: 1. glabella, 2. supraorbital notch, 3. infraorbital foramen, 4. fronto-occipital zone, 5. temporal trigger point, 6. preauricular zone, 7. posterior auricular, 8. masseter muscle, 9. trapezius muscle.

Two injection techniques were employed by an experienced physician in this field: profound intradermal injection at a depth of 2-4 mm and superficial intradermal injection at a depth of 1-2 mm, using sterile single-use needles measuring 0.3 mm × 4 mm and 0.3 mm × 13 mm, respectively. A total of 5 mL was administered per session: 2 mL of 1% lidocaine, 100 U of calcitonin in 1 mL, and 40 mg of piroxicam in 2 mL. All patients had three sessions of mesotherapy at 7 day intervals.

Statistical Analysis

Data were analyzed using IBM SPSS 25.0. Normality was tested using the Shapiro-Wilk test. The Wilcoxon signed-rank test was used for pairwise comparisons, the Friedman test for repeated measures, and the Mann-Whitney U test for gender differences. Effect sizes (r) and 95% confidence intervals were calculated. Significance

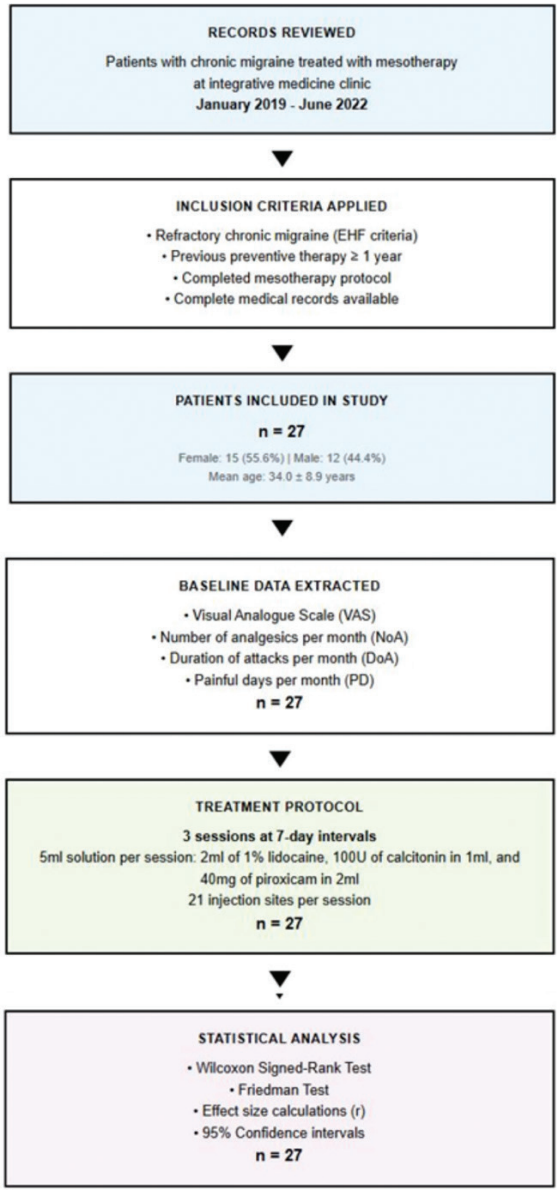

Figure 1. Study flowchart
EHF: European Headache Federation

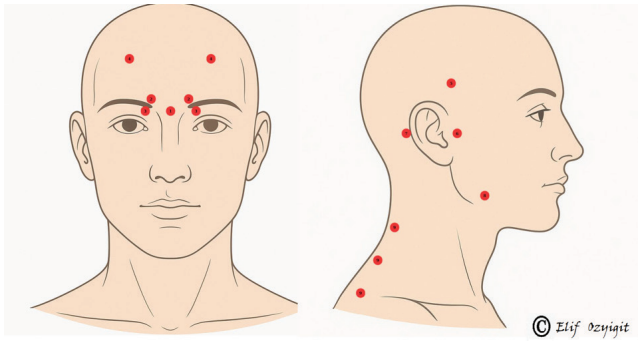

Figure 2. Anatomical sites for mesotherapy application

was set at $p<0.05$. The significance level for all statistical tests was set at $p<0.05$.

Results

The study comprised 27 participants, with 15 females and 12 males. Female patients had a mean age of 31.67±7 years, while male patients had a mean age of 36.9±10.5 years. The overall mean age across both genders was 34±8.936 years.

Mean values and standard deviations at baseline and weeks 4, 8, and 12 are presented in Table 1.

Baseline values were compared with those at weeks 4, 8, and 12 for each parameter (VAS, NoA, DoA, and PD). Pairwise comparisons and the resulting p-values are displayed in Table 2. Baseline means were higher than those at weeks 4, 8, and 12; hence, a statistically significant decrease in VAS, NoA, DoA, and PD values among patients receiving mesotherapy was observed. No adverse events were reported. Temporal changes in treatment outcomes are presented in Figure 4.

The analysis of variance results for dependent variables within the group is presented in Table 3. The Friedman test results indicated statistically significant differences in within-group variances among the groups. This suggests that the treatment effect varied significantly across the time points. The first assessment at 4 weeks post-application showed a notable improvement, and the last assessment at the 12th week showed a gradual reduction in effectiveness. However, the values after this decline did not exceed the initial values.

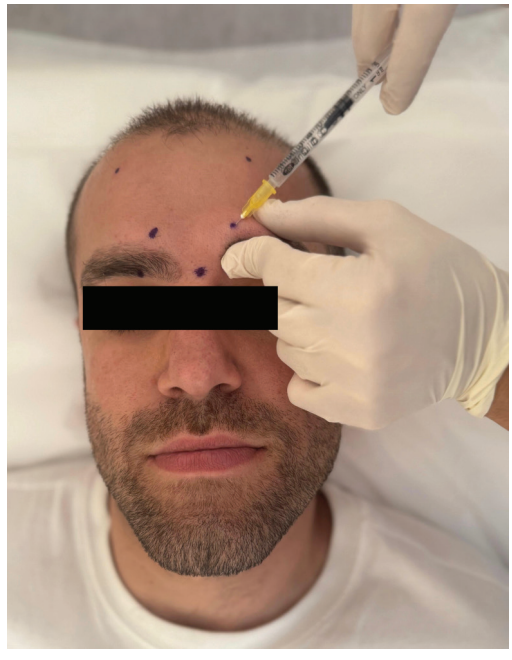

Figure 3. Model application for mesotherapy

Table 1. Group comparisons						
	(Mean ± SD)				Effect size (r)	Confidence interval (95%)
	Baseline	4.Week	8. Week	12. Week		
VAS	7.44±0.801	3.04±0.854	3.48±0.7	5.7±0.823	0.88	0.76-0.94
NoA	7.52±0.893	2.07±0.73	3.85±0.602	5.74±0.526	0.87	0.75-0.93
DoA	19.74±3.182	5.22±2.577	11.63±2.372	16.85±2.553	0.89	0.78-0.95
PD	17.93±3.012	5.59±1.947	9.04±1.48	10.89±1.717	0.89	0.78-0.95
Statistical test: Wilcoxon signed-rank test, effect size: r=Z/√N, where large effect r≥0.5 VAS: Visual analogue scales, NoA: Number of analgesic per month, DoA: Duration of attack per month, PD: Painful days per month, SD: Standard deviation						

Table 2. Comparison of baseline data and weekly data via Wilcoxon signed-rank test						
VAS baseline	VAS 4th week		VAS 8th week		VAS 12th week	
	Z-value	p-value	Z-value	p-value	Z-value	p-value
	-4.593[b]	0.000	-4.612[b]	0.000	-4.620[b]	0.000
NoA baseline	NoA 4th week		NoA 8th week		NoA 12th week	
	Z-value	p-value	Z-value	p-value	Z-value	p-value
	-4.585[b]	0.000	-4.642[b]	0.000	-4.517[b]	0.000
DoA baseline	DoA 4th week		DoA 8th week		DoA 12th week	
	Z-value	p-value	Z-value	p-value	Z-value	p-value
	-4.553[b]	0.000	-4.562[b]	0.000	-4.453[b]	0.000
PD baseline	PD 4th week		PD 8th week		PD 12th week	
	Z-value	p-value	Z-value	p-value	Z-value	p-value
	-4.550[b]	0.000	-4.549[b]	0.000	-4.556[b]	0.000
VAS: Visual analogue scales, NoA: Number of analgesic per month, DoA: Duration of attack per month, PD: Painful days per month						

Table 3. Comparison of related sample variances via friedman test	
Hypothesis	p-value
The distributions of VAS baseline, 4th week, 8th week and 12th week are the same	0.000
The distributions of NoA baseline, 4th week, 8th week and 12th week are the same	0.000
The distributions of DoA baseline, 4th week, 8th week and 12th week are the same	0.000
The distributions of PD baseline, 4th week, 8th week and 12th week are the same	0.000
VAS: Visual analogue scales, NoA: Number of analgesic per month, DoA: Duration of attack per month, PD: Painful days per month	

The analysis of whether the application of mesotherapy yielded different outcomes between male and female patients revealed that there were no significant gender-based differences in response to mesotherapy.

Discussion

The present study demonstrates substantial clinical improvements in CM management through mesotherapy, with effect sizes ranging from 0.86 to 0.90, indicating large clinical effects according to Cohen's criteria. The 59% reduction in VAS scores at 4 weeks (from 7.44 to 3.04) represents a clinically meaningful and substantial improvement in pain intensity.

Chronic migraine is a substantial neurological challenge, yet treatment options remain limited. Clinicians seek interventions that effectively alleviate pain while minimizing the occurrence of severe or intolerable side effects. Topiramate emerges as a pharmacological intervention capable of mitigating the progression to chronic headache in individuals experiencing episodic migraine (10). In addition, administering a greater occipital nerve (GON) block using a combination of lidocaine and methylprednisolone is a reliable alternative for managing refractory CM (11). In a recent randomized controlled trial, Chowdhury et al. (12) reported that combination therapy with topiramate and GON blocks reduced monthly headache days by approximately 6.9 days over a 12-week period in patients with. Our mesotherapy approach demonstrated greater efficacy with a smaller sample size, resulting in a reduction of 12.34 PD at 12

Figure 4. Mesotherapy treatment outcomes: temporal trends
VAS: Visual analogue scale

weeks, suggesting superior therapeutic benefit compared with this established combination therapy (12).

OnabotulinumtoxinA injection is another treatment option reported to show promise in reducing headache severity and frequency in individuals with chronic migraine (13,14). While direct comparison is limited by our retrospective, single-arm design, in contrast to the randomized, placebo-controlled Phase III Research Evaluating Migraine Prophylaxis Therapy trials, our mesotherapy protocol achieved a 69% reduction in painful days within 4 weeks, compared with botulinum toxin's approximately 50% reduction over 24 weeks, suggesting potential advantages in both the magnitude and onset of effects that warrant further investigation in controlled trials.

As an established therapeutic approach in integrative medicine, mesotherapy has been extensively studied in clinical trials for musculoskeletal pain and injuries (8,15-17). The findings of a comparative study by Akbas et al. (18), which assessed the effectiveness of mesotherapy using a mixture of thiocolchicoside, tenoxicam, and lidocaine, demonstrated that mesotherapy was more effective than intravenous dexketoprofen therapy in treating acute migraine attacks without aura. Building on this work on acute migraine attacks, our study is among the first to evaluate mesotherapy as a preventive treatment for CM, demonstrating substantial and sustained benefits over 12 weeks using a different medication combination.

The combination of lidocaine, piroxicam, and calcitonin in the mesotherapy solution potentially offers a multifaceted approach to managing CM. Several studies have investigated the use of lidocaine, particularly through injection or infusion, in various headache disorders (19). Lidocaine, a local anesthetic, can provide immediate pain relief by blocking voltage-gated sodium channels in neuronal membranes, thereby preventing the conduction of impulses along sensory nerves, particularly nociceptive C-fibers, a mechanism crucial for reducing the acute discomfort associated with migraine attacks (20). Piroxicam, a potent cyclooxygenase-2 inhibitor, helps reduce inflammation and pain by inhibiting endogenous prostaglandin production, thereby addressing the inflammatory component often linked to migraine pathophysiology (21). Calcitonin, a hormone known to influence calcium metabolism, has been suggested to have analgesic properties, possibly through its action on central pain pathways (22,23). The synergistic effect of these three components could have resulted in enhanced pain control, reduced frequency and intensity of migraine episodes, and an overall improvement in quality of life for patients, as reported in this study. Future studies should explore the specific mechanisms and long-term benefits of this combination therapy compared with traditional migraine treatments.

The significant findings from the Friedman test indicate meaningful differences in treatment effects across follow-up points, highlighting the temporal dynamics of mesotherapy's efficacy. This suggests that, while mesotherapy is beneficial, its peak effectiveness occurs earlier in the treatment period, necessitating potential consideration of ongoing or integrative treatment strategies to sustain benefits (24,25).

Study Limitations

Although this retrospective cohort study provides valuable insights into the efficacy of mesotherapy in the management of CM, it is essential to acknowledge its limitations, including the lack of a control group and potential biases inherent in retrospective analyses. The small sample size and relatively short follow-up period are additional limitations. Additionally, data on prior migraine treatments were unavailable for all patients, which represents a limitation in fully characterizing baseline clinical status. Despite these limitations, this study is among the few that explore the effectiveness of mesotherapy for treating CM, which may contribute to expanding therapeutic options in multimodal headache management. Additionally, the comprehensive outcome measures used and the large effect sizes reported support the scientific strength of the study.

To further validate these findings and to establish a more robust evidence base, randomized controlled trials are needed to enable direct comparisons of mesotherapy with standard treatments or with placebo, thereby minimizing confounding factors and providing higher-quality evidence regarding treatment efficacy and safety.

Conclusion

Mesotherapy appears to be an effective treatment for managing CM over a 12-week period, showing significant improvements in the duration, intensity, and frequency of pain, as well as a reduction in analgesic use. Large-scale, prospective, randomized controlled trials are needed to better evaluate the effectiveness of this.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Kanuni Sultan Suleyman Training and Research Hospital Ethics Committee (approval no.: KAEK/2022.11.225, date: 21.11.2022).

Informed Consent: Informed consent for publication was obtained from the patients after they agreed that their anonymized case data could be summarized and analyzed.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.O., E.T., Concept: E.O., M.Z., Design: E.O., M.Z., Data Collection or Processing: E.O., E.T., Analysis or Interpretation: E.O., M.Z., M.F.U., Literature Search: E.O., E.T., M.Z., M.F.U., Writing: E.O., E.T., M.Z., M.F.U.

Conflict of Interest: No conflicts of interest were declared by the authors.

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