

Intradermal mesotherapy versus intravenous dexametopfen for the treatment of migraine headache without aura: a randomized controlled trial

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BACKGROUND: Migraine is a prevalent disabling primary headache disorder that is classified into two major types: migraine without aura and migraine with aura. New therapeutic methods to reduce migraine headaches in the emergency department (ED) include intradermal mesotherapy.

OBJECTIVES: Compare the efficacy of intradermal mesotherapy versus a systemic therapy in pain control in patients with headache related to migraine without aura.

DESIGN: Prospective parallel-group randomized controlled trial.

SETTING: University hospital in Turkey.

PATIENTS AND METHODS: Patients 18 years of age and older who were admitted to the ED over a 15-month period with headache related to migraine without aura were eligible for inclusion if they had a VAS score of 4 or above. Patients were randomly allocated to one session of mesotherapy or intravenous dexametopfen. Changes in pain intensity were measured by the score on a visual analog scale (VAS) at 30, 60, and 120 minutes and 24 hours after treatment. Efficacy was also assessed by the need for use of an analgesic drug within 24 hours, by readmission with the same complaint to the ED within 72 hours, and by adverse effect rates.

MAIN OUTCOME MEASURE: Pain intensity on the VAS scale.

SAMPLE SIZE: 148 patients (154 enrolled and treated; 1 patient in the mesotherapy and 5 patients in the systemic therapy group lost to follow up).

RESULTS: Pain intensity on the VAS scale decreased from a median score of 8 to 4 in the mesotherapy group and from 8 to 5 in the systemic therapy group. These differences were statistically significant from baseline for all time intervals ($P=.001$ to 30 minutes, $P=.004$ to 60 minutes, $P=.005$ to 120 minutes, and $P=.002$ to 24 hours). The need to use analgesics and the rate of readmission to the ED were higher in the systemic therapy group ($P=.013$ and $P=.030$, respectively). Adverse effect rates were minimal and similar in the study groups during the one-week follow-up period.

CONCLUSIONS: Mesotherapy is more efficacious than intravenous dexametopfen in the management of acute attack of migraine without aura in the ED.

LIMITATIONS: Unblinded. Valid for assessing short-term pain relief, but not sufficient to predict long-term efficacy. Not generalizable because single center and small sample size.

CONFLICT OF INTEREST: None.

REGISTRATION: ClinicalTrials.gov (NCT04519346)

Migraine is a prevalent primary headache disorder that can cause many disabilities.¹ It has two major types: migraine without aura and migraine with aura. The migraine without aura is the most prevalent subtype of migraine headache, which is seen about for 75% of patients.²

Over one billion people were estimated to have had migraine in 2016, and migraine caused 45.1 million years lost due to disability globally.³ This huge burden also causes social problems and healthcare system issues besides effects on the individual. Migraine patients had a lower health-related quality of life, higher levels of absenteeism from work, work impairment, and activity impairment, and higher healthcare resources utilization in comparison with non-migraine individuals in the European Union (France, Germany, Italy, Spain, United Kingdom).⁴ Of United States adults, 14.2% reported suffering from migraine or severe headache in the past three months in 2012.⁵ Headache or pain in the head was the fourth common cause of visits to the emergency department (ED) between 2009 and 2010, responsible for 3.1% of all ED visits, and 16.7% of all visits for migraine occurred in EDs, in the US.⁵

The acute treatment of migraine in adults includes specific medications such as triptans and dihydroergotamine, nonspecific medications such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, sumatriptan/naproxen combination, acetaminophen/aspirin/caffeine combination, intravenous magnesium, isometheptene compounds, and the antiemetic medications such as prochlorperazine, droperidol, chlorpromazine, and metoclopramide.⁶ Systemic therapy of dexametopfen can provide pain control at 45 minutes to 48 hours and reduce rescue drug need with no significant increase in adverse events in patients with a migraine attack.^{7,8} A double-blind randomized controlled study of 279 migraine patients found that the combination of frovatriptan and dexametopfen was more efficient than frovatriptan alone for the treatment of migraine attacks.⁹ Also there are so many non-pharmaceutical methods in migraine treatment which include non-invasive neuromodulation, nutraceuticals such as riboflavin and magnesium, and behavioral treatment approaches.¹⁰

Mesotherapy may be an efficient treatment method in the treatment of fibromyalgia, gout, headache, neuralgia, low back pain, sports injury, and musculoskeletal pain.¹¹⁻¹⁴ Mesotherapy has a dual mechanism in pain relief, one of which is the process of introducing needles into the skin that stimulates a reflex action by increasing endorphin levels, and the second is the local effect of the drug.¹⁵ Besides, to the best of our knowledge, there is no published study that has compared mesotherapy with any systemic treatment method. We aimed to compare the efficiency of mesotherapy of a cocktail of thiocolchicoside, lidocaine, and tenoxicam with intravenous application of dexametopfen in pain management in patients admitted to ED with headache-related to migraine without aura.

METHODS

This study was a prospective parallel-group randomized controlled trial with restricted randomization generated by the product, Random Allocation Software (RAS)¹⁶ version 2 (<https://random-allocation-software.software.informer.com/2.0/>) with a 1:1 allocation ratio. We conducted the study following the CONSORT checklist¹⁷ and by the rules of the Declaration of Helsinki, at our emergency department from 1 December 2019 to 29 February 2020 after approval was obtained from the Clinical Research Ethics Committee. Also, written informed consent was obtained from all patients included in the study. Our ED has approximately 120000 admissions annually and is a part of a 1400-bed tertiary care hospital. Our department provides regional emergency care for primary and referred patients. The study was registered on ClinicalTrials.gov (NCT04519346).

After a comprehensive medical history and physical examination, patients with headache related to the migraine without aura were eligible for the study if 18 years of age or older and if they had a VAS score of 4 or above. We used the third edition of the International Classification of Headache Disorders (ICHD-3) for migraine description and diagnosis.¹ We included only patients without aura to restrict the confounding effect of the aura on pain perception. We excluded patients who had taken analgesic drugs before admission, had

a visual analogue scale (VAS) score lower than 4 on admission, had diabetes mellitus, had a body mass index (BMI) of >30 kg/m², were pregnant, were in lactation, had active bleeding or bleeding disorder, had an active or recurrent gastrointestinal hemorrhage or ulcer, or history of these conditions, or had a life-threatening or serious disorder. The patients were allocated to two study arms using opaque envelopes to provide allocation concealment, by the sequence list we generated via RAS software.

Mesotherapy was performed with 4- and 6-mm long 30-gauge needles (Meso-relle, Biotekne SRL, Italy) into the pericarotid region, the glabella, and the area between the eyes and ears, and to the area of the head where the pain occurred (such as frontal, parietal, occipital region) for each patient, by a trained and experienced medical doctor. Injections were applied by pinching the skin in the pericarotid region. Two mixtures were prepared for each mesotherapy session. The first mixture consisted of 1 cc (2 mg) thiocolchicoside (Tyoflex, Abdi Ibrahim Pharmaceutical Industry and Trade Co., Turkey), 1 cc (16.2 mg) lidocaine (Aritmal, Osel Pharmaceutical Industry and Trade Co., Turkey), and 1 cc (5 mg) tenoxicam (Oksamen, Mustafa Nevzat Pharmaceuticals Industry Inc., Turkey) for the glabella, the area between the eyes and ears, and the painful area, and the other one consisted of 1 cc (16.2 mg) lidocaine (Aritmal, Osel Pharmaceutical Industry and Trade Co., Turkey) and 1 cc (5 mg) tenoxicam (Oksamen, Mustafa Nevzat Pharmaceuticals Industry Inc., Turkey) only for the pericarotid region. A dose of 0.1-0.2 cc was administered at each point at a 1- to 3-mm depth using a point-by-point intradermal method with a minimum of 25 injections without causing papules (**Figure 1**). The agents and doses in the drug cocktail were found efficient and safe for painkilling in our previous studies.^{12,14} In the systemic therapy group, an intravenous infusion included 50 mg dexketoprofen (Revafen, Haver Pharma Pharmaceutical Co., Turkey) in 100 cc normal saline that was infused over 5 minutes.

Patient sex, age, BMI, and pain duration (minute) were recorded. The migraine pain begins gradually and increases in intensity over time. Therefore, the pain duration refers to the period from the time the VAS score exceeded 4, not from the beginning of pain. The VAS scores at the beginning of the treatment (baseline), and at 30, 60, and 120 minutes, and 24 hours following the treatment were measured with a 10-cm scale ranging between 0 and 10 (0 was the absence of pain and 10 was unbearable pain). There were three primary outcomes: the change in headache intensity or reduction in pain intensity over different time intervals.

The values were obtained by subtracting the VAS scores at 30, 60 and 120 minutes, and 24 hours from the baseline VAS score. A VAS questionnaire given to the patients explained how to perform the measurement. The patients recorded the VAS scores themselves, and we obtained the 3 scores from the questionnaire and by a telephone call for the 24-hour VAS scores. The second primary outcome of the study was any clinically meaningful change (CMC) in headache intensity defined as a reduction of 33% or more in VAS score. We calculated CMC at 30, 60, and 120 minutes, and at 24 hours. Although there are various opinions about changes in pain intensity, a reduction of 33% in pain intensity represents a reasonable breakpoint for defining a meaningful reduction in terms of patients with acute pain. This approach prevents selection bias related to the initial pain intensity of the patients.^{18,19}

The third primary outcome of our study was the need for use of analgesics within 24 hours after treatment. We defined this as a requirement of any type of analgesic for pain killing at any time within 24 hours of treatment, and this was evaluated by patients, subjectively. The final primary outcome of the study was re-admission to the ED. This was defined as the admission to ED with a complaint of headache related to migraine without aura within 72 hours of treatment. The secondary outcome was having a side effect from the treatments defined as the presence of any of the following: diarrhea, dizziness, edema, hypotension, bruising,



Figure 1. Mesotherapy procedure. (A) application to 3 points in the pericarotid region; (B) application to 3 points in glabella; (C, D) application to 6 points between the eye and ear.

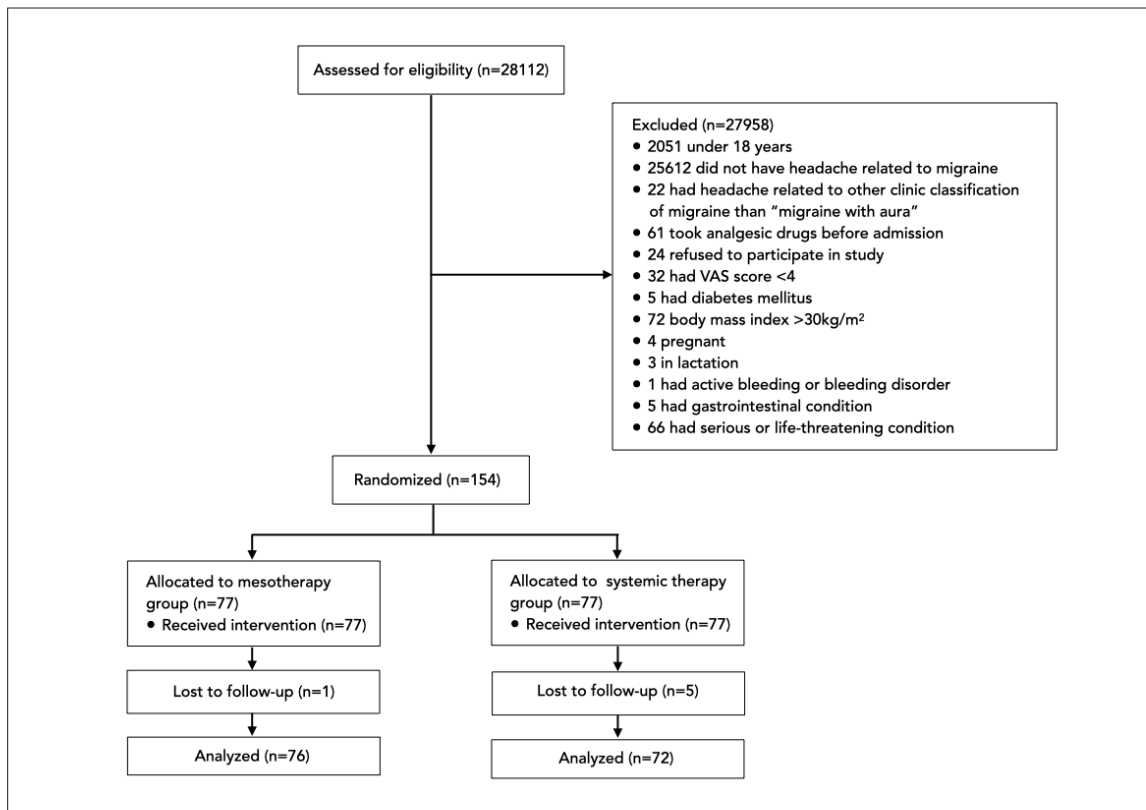


Figure 2. CONSORT flow diagram of study.

localized infections, pruritus, or swelling at the injection sites, nausea and vomiting for the mesotherapy group; and the presence of any of following: diarrhea, dizziness, dry mouth, dyspepsia, hypotension, nausea and vomiting, peptic ulcer bleeding, peptic ulceration, pruritus, urticarial lesion for the dexketoprofen group. The patients were followed-up with daily phone calls for the need to use analgesics, re-admission to ED (they may have been admitted to another ED), and the presence of side effects, and were evaluated with a planned visit to our ED at the end of the one-week follow-up period.

The a priori required sample size was calculated as 70 patients for each study arm, with a median effect size of 0.5 for the VAS score, type 1 error of 0.05, and a power of 0.90 via G*Power 3.1 software.²⁰ Statistical analyses were performed using IBM SPSS version 20 (IBM Corp, Armonk, NY). Descriptive statistics for categorical variables are shown as the frequency and percentage, and the median with interquartile range for numerical variables. The Shapiro-Wilk test and Kolmogorov-Smirnov test were used to evaluate the normality of the distribution of numeric data. The Mann-Whitney U test was used for comparing non-normally distributed numerical variables between the study arms. The Pearson Chi-

square test and Fisher's exact test were used for comparing categorical data among the study groups. $P < .05$ was considered statistically significant.

RESULTS

Patients admitted with any complaint to our ED (n=28 112) were assessed for eligibility. After excluding 27 958 patients, 154 patients were randomized into the study arms (77 to each group). One patient in the mesotherapy group and five in the systemic therapy group were lost to follow-up so that 148 patients (76 in the mesotherapy group, 72 in the systemic therapy group) completed the study (**Figure 2**). The median age was 36.0 years in each group (**Table 1**). BMI and the median duration of pain were similar in the two groups. The median baseline VAS score was 8.0 for both study arms (**Figure 3**).

The decreases in VAS scores were significantly higher in the mesotherapy group than the systemic therapy group for each time interval from baseline (**Table 2**). Also, the presence of CMC in pain intensity was significantly higher in the mesotherapy group than in the systemic therapy group for all periods (**Table 3**). However, five patients in the mesotherapy group and 13 patients

in the systemic therapy group still did not show a clinically significant improvement in pain relief at 24 hours.

Use of analgesics at any time within 24 hours after treatment and the rate of readmission to ED were significantly higher in the systemic therapy group than the mesotherapy group (**Table 4**). Two patients in the mesotherapy group and 4 patients in the systemic therapy group had side effects related to treatment. This difference was not statistically significant during the follow-up. In the mesotherapy group, two patients had local reactions on the injection site; however, one patient had nausea, two patients had vomiting and one patient had dizziness in the systemic therapy group. All side effects were acceptable and managed with proper treatment.

The initial VAS score of the lost to follow-up patient in the mesotherapy group was 7, and the median VAS score of the lost to follow-up patients in systemic therapy group was 8.

DISCUSSION

We found that the administration of analgesics with mesotherapy was associated with clinically valuable pain relief and acceptably side effects in patients with headache related to migraine without aura in the ED setting. We included migraine patients because they have higher pain intensity that can lead to more frequent NSAIDs usage and a higher risk of the side effects of NSAIDs. A cocktail of thicocolchicoside, lidocaine, and tenoxicam mesotherapy application had both statistically and clinically significant greater decreases in pain intensity with less need to use analgesics within 24 hours and fewer readmissions with the same complaint to ED within 72 hours after treatment. Side effects were similar when compared to systemic dexametopofen administration.

Headache is frequently unilateral, throbbing, and aggravated by physical activity or head movement in migraine patients.¹ The pain intensity varies between moderate and severe during attacks, and the median duration of headache ranges from 4 to 72 hours in adults. Migraine patients can feel pain in any part of the head, but most frequently the pain is in the posterior cervical and trapezius regions.²¹ Migraine pain can occur at any time of the day, but most frequently occurs at night during sleep and/or upon awakening in the morning.²² The 1-year prevalence of migraine is nearly 12% in the general population,²³ and the lifetime prevalence is 33% in women and 13% in men.²⁴ Migraine is associated with overuse of healthcare resources such as much more visits to EDs.²⁵ The ED often becomes the primary healthcare setting to manage moderate-to-severe migraine pain. Different treatments have been recommended for migraine headache in EDs.^{6,26} However,

Table 1. Demographics and baseline characteristics (n=148).

Characteristics	Mesotherapy (n=76)	Systemic therapy (n=72)
Age (years)	36 (30.0-56)	36 (33-56)
Sex (female)	32 (42.1)	31 (43.1)
Body mass index (kg/m ²)	24.5 (23.2-25.0)	24.5 (23.1-25.0)
Duration of pain (minute)	130.0 (90.0-160.0)	125.0 (75.0-150.0)
Baseline VAS score	8 (6-10)	8 (6-10)

Data are n (%) or median (interquartile range). VAS: visual analog scale

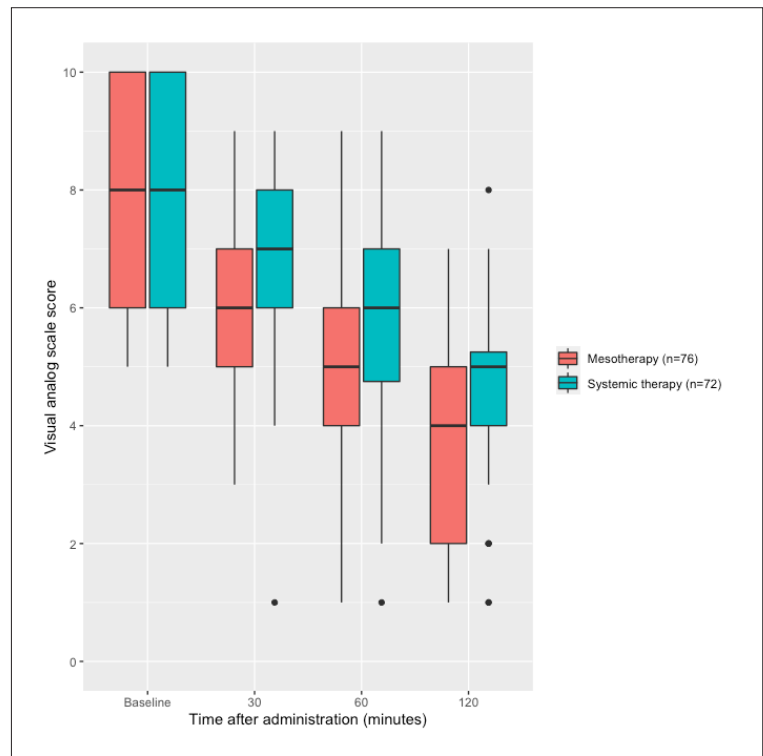


Figure 3. Visual analog scale scores at baseline and after administration of treatment (median, interquartile range, minimum and maximum).

Table 2. Change in median values of visual analog scores in the treatment groups.

Time period	Mesotherapy (n=76)	Systemic therapy (n=72)	P
Baseline to 30 min	2.0 (1.0-3.0)	1.0 (0.0-1.0)	.001
Baseline to 60 minutes	3.0 (2.0-5.0)	2.0 (1.0-3.0)	.004
Baseline to 120 minutes	4.0 (3.0-6.0)	3.0 (2.0-4.0)	.005
Baseline to 24 h	5.0 (4.0-7.0)	4.0 (3.0-5.0)	.002

Data are median (interquartile range). Mann-Whitney U test.

Table 3. Clinically meaningful changes in visual analog scale scores.

Time period		Mesotherapy	Systemic therapy	P
Baseline to 30 min	CMC +	33 (43.4)	3 (4.2)	<.001
	CMC -	43 (56.6)	69 (95.8)	
Baseline to 60 minutes	CMC +	48 (63.2)	27 (37.5)	.002
	CMC -	28 (36.8)	45 (62.5)	
Baseline to 120 minutes	CMC +	63 (82.9)	48 (66.7)	.023
	CMC -	13 (17.1)	24 (33.3)	
Baseline to 24 h	CMC +	71 (93.4)	59 (81.9)	.033
	CMC -	5 (6.6)	13 (18.1)	
Total		76 (100.0)	72 (100.0)	

Data are n (%). CMC: Clinically meaningful (33% or more) improvement (+) or worsening or no change (-) in pain intensity. Pearson Chi-square test.

treatment choices can be based on the experience of emergency physicians, patient preferences, and the patient medical conditions.²⁷ The use of intravenous fluids, dopamine receptor antagonists, ketorolac, and dexamethasone has increased, while narcotic usage has decreased over the years.²⁸

Another important aspect of pain management with migraines is the whether the reduction in pain intensity is meaningful.¹⁸ A breakpoint of 33% for the percentage of reduction in pain intensity from baseline values was found plausible as meaningful pain relief,^{18,19} but Mammucari et al³¹ reported that patients declare the pain relief as meaningful when reduction is at least 50% from baseline. Assuming that a reduction of 33% or more in headache intensity was clinically meaningful in this study, the changes in VAS scores favored mesotherapy over intravenous injection of dexketoprofen.

The guidelines of the European Federation of

Neurological Societies recommend triptans, acetylsalicylic acid, naproxen, ibuprofen, diclofenac, and paracetamol as the first-line medication options.²⁹ Yang et al⁷ reviewed and performed a meta-analysis of five studies published between 2014 and 2016, in which dexketoprofen 50 mg compared with placebo or frovatriptan 2.5 mg combined with dexketoprofen 37.5 mg compared with frovatriptan 2.5 mg plus placebo. They reported that dexketoprofen was a good treatment option in pain relief in patients with migraine, with a reduced need for rescue drugs, and with no significant increase in side effects.⁷ Many studies have investigated the efficacy of mesotherapy on pain relief in health conditions other than migraine.^{12,14,30,31} Those studies reported that mesotherapy can be a good treatment option for pain relief when compared to different analgesics. Nevertheless, there is no published study that has compared mesotherapy with systemic use of analgesics for the efficiency or safety of the treatment of migraine headache. Therefore, to the best of our knowledge, our trial is the first study in which mesotherapy has been compared with an NSAID.

A dual mechanism is thought to be involved with mesotherapy in pain treatment: the first is a reflex action via increasing endorphin levels by the physical stimulations of the injections, and the second is the local effect of the agents.^{15,32} In one study, treatment with repetitive transcranial magnetic stimulation decreased pain, which was associated with an increase in β endorphin level that was initially lower in patients with migraine.³³ This mechanism may be a possible explanation for our results. Anesthetic agents, muscle relaxants, analgesic agents, and anti-inflammatory drugs have been used alone or as a cocktail for analgesia using the mesotherapy technique.³² These drugs might chemically or physi-

Table 4. Other outcome measures.

		Mesotherapy	Systemic therapy	P
Need to use analgesic	No	68 (89.5)	53 (73.6)	.013 ^a
	Yes	8 (10.5)	19 (26.4)	
Re-admission to ED	No	75 (98.7)	65 (90.3)	.030 ^b
	Yes	1 (1.3)	7 (9.7)	
Any adverse effect	No	74 (97.4)	68 (94.4)	.224 ^a
	Yes	2 (2.6)	4 (5.6)	
Total		76 (100.0)	72 (100.0)	

Data are n (%). ^aPearson chi-square test was used. ^bFisher's exact test was used.

cally stimulate the endorphin system and the peripheral immune system.³⁴ The pain relief might be explained by all these phenomena. However, more detailed studies are needed to show the effectiveness of mesotherapy more clearly.

Mesotherapy has transient side effects such as ecchymosis, allergic reactions, and minimal local infectious complications that are possibly related to inadequate aseptic measures or practical failures.³⁵⁻³⁷ Correct mesotherapy application requires a clinically skilled applicator and adequate hygiene standards.³¹ We have clinical experience with mesotherapy and trigger point injection applications in patients with pain related to different health conditions.^{12,14,38} Our mesotherapy treatment mixture can be intradermally injected without complication, based on our previous clinical experience.^{12,14}

Our study has several limitations. In the mesotherapy procedure, the usage of a mixture of different pharmacological agents or inadequate aseptic measures can cause local reactions,³⁷ but there was no notable local reaction in this study nor in any prior studies.^{12,14} Our results are valid in the short term, but they are probably not sufficient to predict the long-term efficacy of mesotherapy on pain control. We included only patients with migraine without aura because the study focused on pain relief. However, migraine with aura presents with visual, sensory, or other central nervous system symptoms

that are usually followed by a headache.¹ Also, there are other limitations related to the nature of the design of the study and the lack of blinding because of the need to protect patients from possible side effects of invasive procedure. Because the study was single-center with a relatively small sample size, the results might not be generalizable to a larger population. One patient in the mesotherapy group and 5 patients in the systemic treatment group dropped out of the study before the VAS measurements, which were the primary outcome of the study. Hence, using intention-to-treat analysis is impossible with missing outcome data. Treating missing outcome data with imputation methods such as "last value carried forward" and then performing ITT analysis could be considered as an option. Because of the concern that this method might pose a risk of overestimation and since there was no treatment protocol deviation among the patients, the per-protocol analysis was performed in the study.

In conclusion, mesotherapy is more efficacious than intravenous dexketoprofen in the management of acute attack of migraine without aura in the ED. Randomized controlled clinical trials with a larger sample size should be conducted to confirm the results of our study using long-term outcomes on pain relief, while also assessing any improvement in the quality of healthcare, and patient satisfaction.

REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018 Jan;38(1):1-211. doi: 10.1177/0333102417738202. PMID: 29368949.
2. Shankar Kikkeri N, Nagalli S. Migraine with Aura. 2020 Jul 5. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. PMID: 32119498.
3. Stovner LJ, Nichols E, Steiner TJ, Abd-Allah Foad, Abdelalim A, Al-Raddadi RM, et al. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology. 2018;17(11):954-76.
4. Vo P, Fang J, Bilitou A, Laflamme AK, Gupta S. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. The journal of headache and pain. 2018;19(1):82.
5. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. Headache. 2015;55(1):21-34.
6. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American headache society evidence assessment of migraine pharmacotherapies. Headache. 2015;55(1):3-20.
7. Yang B, Xu Z, Chen L, Chen X, Xie Y. The efficacy of dexametoprolol for migraine attack: A meta-analysis of randomized controlled studies. Medicine. 2019;98(46):e177734.
8. Gungor F, Akyol KC, Kesapli M, Celik A, Karaca A, Bozdemir MN, et al. Intravenous dexametoprolol vs placebo for migraine attack in the emergency department: A randomized, placebo-controlled trial. Cephalalgia : an international journal of headache. 2016;36(2):179-84.
9. Tullo V, Valguarnera F, Barbanti P, Cortelli P, Sette G, Allais G, et al. Comparison of frovatriptan plus dexametoprolol (25 mg or 37.5 mg) with frovatriptan alone in the treatment of migraine attacks with or without aura: a randomized study. Cephalalgia: an international journal of headache. 2014;34(6):434-45.
10. Puledda F, Shields K. Non-Pharmacological Approaches for Migraine. Neurotherapeutics: the journal of the American Society for Experimental NeuroTherapeutics. 2018;15(2):336-45.
11. Palermo S, Riello R, Cammardella MP, Carossino D, Orlandini G, Casigliani R, et al. TENS + mesotherapy association in the therapy of cervico-brachialgia: preliminary data. Minerva anestesologica. 1991;57(10):1084-5.
12. Akbas I, Kocak AO, Kocak MB, Cakir Z. Comparison of intradermal mesotherapy with systemic therapy in the treatment of low back pain: A prospective randomized study. The American journal of emergency medicine. 2020;38(7): 1431-1435
13. Menkès CJ, Laoussadi S, Kac-Ohana N, Lasserre O. Controlled trial of injectable diclofenac in mesotherapy for the treatment of tendinitis. Revue du rhumatisme et des maladies osteo-articulaires. 1990;57(7-8):589-91.
14. Kocak AO. Intradermal mesotherapy versus systemic therapy in the treatment of musculoskeletal pain: A prospective randomized study. The American journal of emergency medicine. 2019;37(11):2061-5.
15. Mammucari M, Gatti A, Maggiori S, Bartoletti CA, Sabato AF. Mesotherapy, definition, rationale and clinical role: a consensus report from the Italian Society of Mesotherapy. European review for medical and pharmacological sciences. 2011;15(6):682-94.
16. Saghaei M. Random allocation software for parallel group randomized trials. BMC medical research methodology. 2004; 4:26.
17. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ (Clinical research ed). 2010;340:c332.
18. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. The journal of pain. 2003;4(7):407-14.
19. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain. 2000;88(3):287-94.
20. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior research methods. 2007;39(2):175-91.
21. Kelman L. Pain characteristics of the acute migraine attack. Headache. 2006;46(6):942-53.
22. Gori S, Lucchesi C, Baldacci F, Bonuccelli U. Preferential occurrence of attacks during night sleep and/or upon awakening negatively affects migraine clinical presentation. Functional neurology. 2015;30(2):119-23.
23. Merikangas KR. Contributions of epidemiology to our understanding of migraine. Headache. 2013;53(2):230-46.
24. Bille B. A 40-year follow-up of school children with migraine. Cephalalgia: an international journal of headache. 1997;17(4):488-91.
25. Dodick DW. Migraine. Lancet. 2018;391(10127):1315-30.
26. Orr SL, Aubé M, Becker WJ, Davenport WJ, Dilli E, Dodick D, et al. Canadian Headache Society systematic review and recommendations on the treatment of migraine pain in emergency settings. Cephalalgia: an international journal of headache. 2015;35(3):271-84.
27. Meredith JT, Wait S, Brewer KL. A prospective double-blind study of nasal sumatriptan versus IV ketorolac in migraine. The American journal of emergency medicine. 2003;21(3):173-5.
28. Ruzek M, Richman P, Eskin B, Allegra JR. ED treatment of migraine patients has changed. The American journal of emergency medicine. 2019;37(6):1069-72.
29. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine—revised report of an EFNS task force. European journal of neurology. 2009;16(9):968-81.
30. Conforti G, Capone L, Corra S. Intradermal therapy (mesotherapy) for the treatment of acute pain in carpal tunnel syndrome: a preliminary study. The Korean journal of pain. 2014;27(1):49-53.
31. Mammucari M, Gatti A, Maggiori S, Sabato AF. Role of mesotherapy in musculoskeletal pain: opinions from the Italian society of mesotherapy. Evidence-based complementary and alternative medicine: eCAM. 2012;2012:436959.
32. 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.
33. Misra UK, Kalita J, Tripathi GM, Bhoi SK. Is β endorphin related to migraine headache and its relief? Cephalalgia : an international journal of headache. 2013;33(5):316-22.
34. Stein C, Machelska H, Schäfer M. Peripheral analgesic and antiinflammatory effects of opioids. Zeitschrift für Rheumatologie. 2001;60(6):416-24.
35. Correa NE, Catano JC, Mejia GI, Realpe T, Orozco B, Estrada S, et al. Outbreak of mesotherapy-associated cutaneous infections caused by Mycobacterium chelonae in Colombia. Japanese journal of infectious diseases. 2010;63(2):143-5.
36. Galmes-Truyols A, Gimenez-Duran J, Bosch-Isabel C, Nicolau-Riutort A, Vanrell-Berga J, Portell-Arbona M, et al. An outbreak of cutaneous infection due to Mycobacterium abscessus associated to mesotherapy. Enfermedades infecciosas y microbiología clinica. 2011;29(7):510-4.
37. Outbreak of mesotherapy-associated skin reactions—District of Columbia area, January–February 2005. MMWR Morbidity and mortality weekly report. 2005;54(44):1127-30.
38. Kocak AO, Ahiskalioglu A, Sengun E, Gur STA, Akbas I. Comparison of intravenous NSAIDs and trigger point injection for low back pain in ED: A prospective randomized study. The American journal of emergency medicine. 2019;37(10):1927-31.