



Intradermal mesotherapy versus systemic therapy in the treatment of musculoskeletal pain: A prospective randomized study

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ABSTRACT

Introduction: Acute musculoskeletal injuries are one of the most common painful presentation when admission to the emergency department. The aim of the study is to compare the tenoxicam mesotherapy with intravenous dextetopfen in pain control in patients with acute musculoskeletal injury.

Methods: This parallel randomized controlled trial was conducted with the patients admitted to the emergency department with musculoskeletal injury. Intravenous dextetopfen was administered to the control group, and mesotherapy treatment was performed to the other group. Differences between 10th, 30th, 60th and 120th minutes VAS scores and on the admission VAS score, clinically meaningful change in pain intensity, and adverse effect of the procedures were compared among groups.

The results: The differences in VAS scores and the presence of clinically meaningful change in pain intensity were statistically significantly higher in mesotherapy group than the systemic therapy group in all time periods. During one-week follow-up period, there was no reported adverse effect neither in mesotherapy group nor in the systemic therapy group.

Conclusions: The mesotherapy treatment may be superior than the systemic therapy for pain relief in musculoskeletal injury in short term follow-up in emergency department settings.

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1. Introduction

Acute musculoskeletal injuries are one of the most common painful presentations for admission to the emergency department (ED), and it is estimated to compose up to 10% of ED visits [1,2]. Pain control is an essential component of management of patients with acute injury and other acute visits to ED. Acute visits to ED can induce anxiety and fear, which are due to the unplanned nature of patient attendance, which can exacerbate the experience of pain intensity [1]. Therefore, pain management provides reduced anxiety and fear, improved patient satisfaction and patient comfort [3].

Systemic pharmacological drugs are the mainstay of therapy for pain control in patients with acute injury [4]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are the most commonly prescribed medications for providing pain relief, the addition of an opioid analgesic is often necessary for more severe pain in patients with cancer or postoperative pain [4,5]. NSAIDs, which are commonly used to control the musculoskeletal pain, have substantial side effects, especially in patients with underlying health problems [2]. They can lead to serious gastrointestinal (GI), cardiac and renal complications, particularly if taken inappropriately [2]. NSAIDs are generally believed to be safe, people do not

have enough information about NSAIDs and their side effects, are commonly used above recommended dose or used concomitantly with other drugs [6]. They are also easily accessible over the counter drugs, and higher dose can be purchased with a medical prescription and these factors contribute to the risk of adverse effects. The Food and Drug Administration and multiple medical societies specify that NSAIDs should be used at the lowest effective dose for the shortest duration needed to achieve a therapeutic effect [6].

Local pharmacological therapy, if effective and reliable, represents an acceptable alternative to systemic NSAIDs for the treatment of musculoskeletal injury [7]. Mesotherapy is the practice of using microinjections of medications into the superficial layer of the skin to treat pain in a specific part of body [8]. The objective of mesotherapy is to modulate the pharmacokinetics of the injected substance and to provide the prolonged effects with intradermal injections of small amount of active substance at the applied area [7]. On the other hand, a local pharmacological effect can be achieved without the need for high systemic concentration [9]. The efficacy of mesotherapy, particularly in the treatment of chronic musculoskeletal pain, was evaluated in a review published by Mammucari et al. and they concluded overall results suggest that mesotherapy provides clinical benefits and more importantly is well tolerated [7]. It was studied in patients with arthritis, with low back pain, with cervicobrachialgia, with gonarthrosis, with

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calcific tendinitis and with carpal tunnel syndrome [7,8]. Multiple mesotherapy sessions were used in these patients suffering chronic pain [7]. The aim of the presented study was to evaluate the effects of one-session application of tenoxicam mesotherapy for pain control, in patients with acute musculoskeletal injury.

2. Methods

2.1. Study design and setting

The study was designed as a prospective parallel randomized controlled trial using restricted randomization via Random Allocation Software (RAS) [10], with random permuted blocks of 4 and an allocation ratio of 1:1 according to the CONSORT guidelines [11]. The study was carried out in accordance with the Declaration of Helsinki. Following the approval of the Clinical Research Ethics Committee of the Atatürk University on 19.09.2018, the study was conducted at Emergency Department of the Atatürk University Training and Research Hospital, between 01.10.2018 and 31.10.2018. The written informed consent was obtained from all patients.

The hospital is a regional, tertiary level, university hospital with a 1400 bed capacity, and approximately, 120,000 patients are admitted to the ED annually.

2.2. Sample size and patients

A-priori required sample size was calculated as 37 patients in each group (74 patients with 1:1 allocation ratio), with a large effect size of 0.6, type 1 error of 0.05 and a power of 0.80 using GPower 3.1 software [12].

Initially, a complete patient history and full physical examination was performed. Then, all patients were evaluated for eligibility according to the inclusion and exclusion criteria. The inclusion criteria of the study were: (1) 18 years and older age, and (2) admission to Emergency Department (ED) with musculoskeletal injury related pain. The exclusion criteria of the study were: (1) having multiple sites injury, (2) having traumatic fractures (extremity fracture, skull fracture, rib fracture, etc.), (3) having a serious or life-threatening condition (heart attack, stroke, intracranial hemorrhage, pneumothorax, cardiac tamponade, hemothorax, flail chest, etc.).

Patients were allocated to the treatment arms: the systemic therapy group and the mesotherapy group according to the sequence list which was generated using RAS software. A research assistant helped to the allocation using sealed, opaque envelopes to ensure allocation concealment.

2.3. Treatment procedures

50 mg dextketoprofen (Revafen, Haver Pharma Pharmaceutical Co., Turkey) in 100 cc isotonic solution was administered to the patients in the systemic therapy group via intravenous route for 5 min.

The mesotherapy was performed using disposable 4 mm and 6 mm long 30 Gauge needles (Meso-relle, Biotekne SRL, Italy) by an experienced and trained physician. For each treatment session a mixture containing 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) was prepared. A 0.1–0.2 cc of this pharmacological mixture was administered to each injection site injected with a depth of 1–3 mm and without causing papules using point by point intradermal method (Fig. 1).

2.4. Variables and outcomes

Age, sex and body mass index (BMI) of the patients, duration of pain, mechanism of injury and anatomic location of injury were recorded. VAS scores were measured on admission, and at 10th, 30th, 60th and 120th minutes after treatment with a 10-cm visual analogue scale ranging between 0 and 10. The value 0 was defined as absence of pain and 10 as intolerable pain.

There are two primary outcomes of the study. First one is the change in pain intensity, which was determined as delta value of VAS scores at 10th, 30th, 60th and 120th minutes. The delta values were obtained by subtracting the VAS scores at 10th, 30th, 60th and 120th minutes from the VAS score on admission. The second primary outcome of this study is clinically meaningful change in pain intensity, which was defined as 33% or more reduction in VAS score at 10th, 30th, 60th and 120th minutes. Although there are different opinions on interpreting the changes in VAS scores,



Fig. 1. An example of a mesotherapy procedure. Trained expert is performing mesotherapy to a patient's ventral forearm.

the 33% reduction in pain intensity represents a plausible cut-off value for defining that a change is meaningful by the patients suffered with acute pain, and is not biased by the initial pain intensity levels [13,14].

The secondary outcome of the study is the presence/absence of adverse effect of two treatment methods. Having dry mouth, nausea and vomiting, diarrhea, dyspepsia, peptic ulceration, peptic ulcer bleeding, urticarial lesion, pruritus, dizziness or sleepiness were defined as presence of adverse effect for the systemic therapy group. Having nausea and vomiting, diarrhea, edema, localized infections, pruritus, bruising or swelling at the injection sites were defined as presence of adverse effect for the mesotherapy group. We followed the patients for one week after the treatment for development of any adverse effects. Patients were interviewed daily by telephone, and evaluated at the end of one week after treatment.

2.5. Statistical analysis

Statistical analyses were performed using SPSS version 20 statistical package program (IBM Corp. in Armonk, NY). Descriptive data are presented as mean with standard deviation, and median with interquartile range for numerical variables, the frequencies and percentage for categorical variables. Shapiro-Wilk and Kolmogorov – Smirnov tests were used to evaluate the distribution

of the data. Independent samples *t*-test was used for comparing normally distributed data, and the Mann–Whitney *U* test was used for comparing non-normally distributed data between two study groups. Pearson Chi-square test and Fisher's exact tests were used for comparing categorical variables. $p < 0.05$ was considered as statistically significant level.

3. Results

The study was conducted with the patients admitted to ED with acute musculoskeletal injury. A total of 9208 patients who admitted with any complaint to ED were enrolled and assessed for eligibility in the study. After excluding 9112 patients, 96 patients were randomized into the mesotherapy group and the systemic therapy group. In the mesotherapy group, 10 patients withdrew from study just after allocation (before the treatment), because they were informed about that they were allocated to the mesotherapy arm, and they didn't want to receive mesotherapy. Also these patients' data were not gathered. There was no lost-to follow up in study groups, and 86 patients completed the study (38 were in the mesotherapy group, 48 were in the systemic therapy group) (Fig. 2).

The median age were 31.0 years and 29.0 years; the females were 55.3% and 50.0% of the groups; the median BMI were

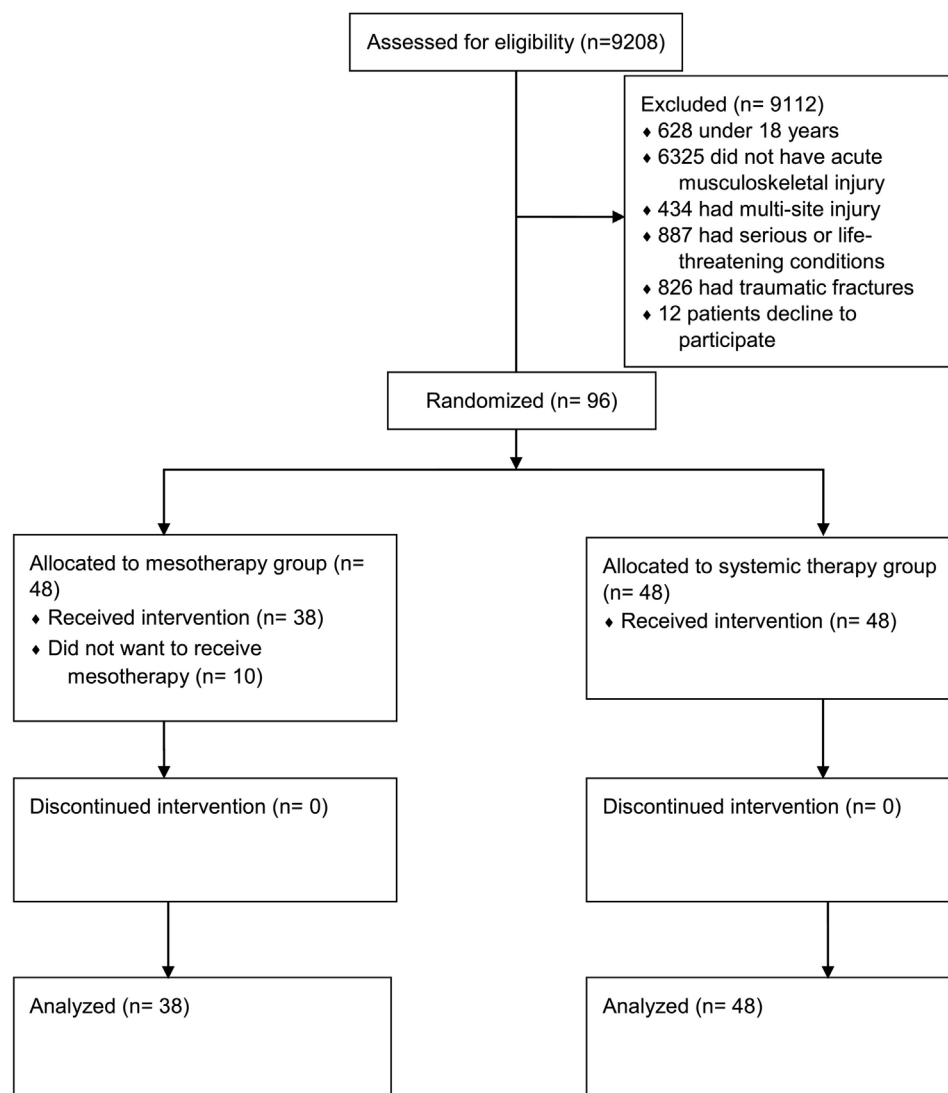


Fig. 2. CONSORT flow diagram of study.

Table 1
Demographics and baseline characteristics.

Characteristics	Mesotherapy group (n = 38)	Systemic therapy group (n = 48)
Age (years), median (IQR)	31.0 (13.5)	29.0 (8.8)
Sex (female), n (%)	21 (55.3)	24 (50.0)
BMI (kg/m ²), median (IQR)	24.5 (2.8)	23.9 (3.8)
Duration of pain (minute), median (IQR)	120.0 (202.5)	147.5 (203.8)
Mechanism of injury, n (%)		
Fall	32 (84.2)	39 (81.2)
Sports injury	4 (10.5)	5 (10.4)
Vehicle accident	2 (5.3)	4 (8.3)
Anatomic location of injury, n (%)		
Ventral arm	7 (18.4)	13 (27.1)
Dorsal arm	8 (21.1)	9 (18.8)
Ventral forearm	4 (10.5)	4 (8.3)
Dorsal forearm	2 (5.3)	2 (4.2)
Ventral leg	17 (44.7)	20 (41.7)

IQR: Interquartile range, BMI: Body mass index.

24.5 kg/m² and 23.9 kg/m²; the median duration of symptoms were 120.0 min and 147.5 min in the mesotherapy group and the systemic therapy group, respectively. The leading mechanism of injury was fall, the second one was sports injury and the third was vehicle accident in both two groups. (Table 1).

The mesotherapy group had lower pain intensity than the systemic therapy group. The delta values of VAS scores were statistically significantly higher in the mesotherapy group than the systemic therapy group in T₀-T₁ period, T₀-T₂ period, T₀-T₃ period, and T₀-T₄ period (Table 2).

The presence of clinically meaningful change in the mesotherapy group was statistically significantly higher than in the systemic therapy group during all time period (Table 3). During one-week follow-up period, there was no reported adverse effect neither in patients in the mesotherapy group nor in patients in the systemic therapy group (data not shown).

4. Discussion

The steady increase in overall ED visits has been reported in United States and most of ED visits are due to patients seeking relief from their pain [4,15–17]. A systematic review -most of the trials included are observational studies and some of them are randomized studies- and several published trials support that the mesotherapy could be a valuable therapeutic option in the treatment of painful conditions, and most of our knowledge on mesotherapy results from the studies that evaluate the effectiveness of pain control in patients with chronic pain [7,9,18,19]. The mesotherapy has been applied more than one session in these chronic pain conditions [7]. However, there are few studies evaluating the effectiveness of one session mesotherapy in acute musculoskeletal pain [7]. In our study, we applied one-session, tenoxicam and thiocolchicoside with lidocaine were delivered in mesotherapy, in patients with acute musculoskeletal injury and

Table 3
Comparison of clinically meaningful change in VAS scores

		Mesotherapy group, n (%)	Systemic therapy group, n (%)	p
T ₀ -T ₁	CMC +	33 (86.8)	16 (33.3)	<0.001
	CMC -	5 (13.2)	32 (66.7)	
T ₀ -T ₂	CMC +	36 (94.7)	26 (54.2)	<0.001
	CMC -	2 (5.3)	22 (45.8)	
T ₀ -T ₃	CMC +	37 (97.4)	37 (77.1)	0.006
	CMC -	1 (2.6)	11 (22.9)	
T ₀ -T ₄	CMC +	38 (100.0)	43 (89.6)	0.049
	CMC -	0 (0.0)	5 (10.4)	
Total		38 (100.0)	48 (100.0)	

CMC: Clinically meaningful change.

compared the mesotherapy to the systemic intravenous administration of 50 mg of dextketoprofen. Clinically significant pain relief (33% or more change in VAS score) was observed in all patients in the mesotherapy group and in 43 patients (89.6%) in the systemic therapy group, at the 120th-minute evaluation, and the mesotherapy was found more effective in terms of pain reduction than systemic administration. These results are in accordance with previously published studies showing the local administration of NSAIDs via mesotherapy was more effective than the systemic administration [7,9].

Although NSAIDs are some of the most commonly used medications, they are not suitable for all patients and may cause serious side effects, especially in elderly patients and the patients with chronic health problems. Potential adverse effects of NSAIDs are gastrointestinal side effects, nephrotoxicity, bronchospasm and thrombotic cardiovascular events [2]. In many countries NSAIDs are freely available over the counter, however, there is still a lack of awareness about these drugs and their side effects. NSAIDs can be easily and inadvertently misused [6,20]. Therefore, potential side effects of NSAIDs alert the physicians to use them for the shortest duration possible or focus on an alternative use [2,20]. The mesotherapy allows the drug to diffuse into the applied region and to have a prolonged effect at low doses [7]. In our study, no adverse effects were reported by patients in both groups. However, a small number of young patients were involved in our study and our results might not be representative of the general population.

Before using intradermal therapy, or other therapies, a validated scale should be used to classify pain based on the type and intensity [7]. Pain is typically assessed by self-report of patients, as a subjective phenomenon [3]. VAS score of patients in our study was 5 or more and they had moderate or severe pain. The question of clinical significance of changes in pain rating has been examined in relatively little research [13,21,22]. A 33% decrease in pain intensity and an absolute decrease of 2 on a 0 to 10 numeric rating scale were found the best balance between sensitivity and specificity [13,14]. In our study, we compared the delta value of VAS score at 15, 30, 60 and 120 min after therapy in both group. For the patients in the mesotherapy group, all delta values were significantly higher than the systemic therapy group at four assessment period. In addition,

Table 2
Comparison of delta values of VAS scores

Time period		Mesotherapy group (n = 38)	Systemic therapy group (n = 48)	p
T ₀ -T ₁	Mean ± SD	4.13 ± 1.55	1.54 ± 1.15	<0.001
	Median (IQR)	4.00 (2.00)	1.00 (2.00)	
T ₀ -T ₂	Mean ± SD	5.84 ± 2.15	2.81 ± 1.83	<0.001
	Median (IQR)	6.00 (2.25)	2.50 (2.75)	
T ₀ -T ₃	Mean ± SD	6.53 ± 2.25	3.94 ± 1.94	<0.001
	Median (IQR)	7.00 (3.00)	4.00 (2.00)	
T ₀ -T ₄	Mean ± SD	7.10 ± 2.08	4.89 ± 1.90	<0.001
	Median (IQR)	7.00 (3.00)	5.00 (2.00)	

SD: standard deviation, IQR: Interquartile range.

tion, the number of patients who had 33% or more decrease in VAS score were significantly higher in the mesotherapy group than the systemic therapy group at 15, 30, 60 and 120 min. These findings suggest that the mesotherapy is more effective and this effect begins earlier than systemic administration of NSAIDs. However, a mixture of drugs was administered in the mesotherapy group and that should be taken into consideration for overall results obtained. Previous studies demonstrated that administration of drugs via mesotherapy into dermis slowly achieves higher local concentration in the underlying tissue, as compared to systemic administration. Administered drugs via mesotherapy exert local effects close the inflammatory cells, sensory fibers and vascular mediators. Furthermore, microinjections facilitate the rebalancing of nociceptive system and as yet not well-understood local actions [7–9]. All these phenomena can explain the pain relief reported by patients and should be supported by comprehensive studies.

Adverse effects at the site of injection have been reported in the literature such as urticarial, lichenoid drug eruptions and psoriasis [19,23]. If the mesotherapy is not performed with a quality controlled substance, and is performed using inadequately sterilized equipment or contaminated during handling, there can be a predisposition to local infections at the injection region [24]. The nontuberculous mycobacteria were reported as a cause of localized infections after intradermal therapy [24,25]. No evidence of local reactions or no local infections were found in our study [19].

5. Limitations

Our study has several notable limitations. As mentioned above our study includes a small number of young patients and our results are not generalizable to older people or people with chronic health conditions. The mesotherapy was applied for one session in our study and our patients were observed for a short follow-up period. Multiple doses of mesotherapy provide an opportunity to perform extended observation periods. The use of a mixture of drugs for local therapy is a concern due to the increased risk of pharmacological interactions, but no evidence of local reactions was determined in our study. In addition, the nature of the design of this surgical study does not allow the blinding, and that should be kept in mind when interpreting the results.

6. Conclusions

The ultimate aim of pain management in acute musculoskeletal injury is to reduce pain. Reducing patient's anxiety, shortening hospital stay, enhancing patient satisfaction and quality of life are secondary gains of the pain management. Our results suggest that the response to the mesotherapy may be superior than the systemic therapy in the short term follow up. This alternative therapy could be a reliable option as a complementary treatment in an overall treatment planning in patients with musculoskeletal injury.

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