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Iontophoresis in lateral epicondylitis: a randomized, double-blind clinical trial

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Background: Lateral epicondylitis (LE) is a painful condition typically caused by excessive use of tendons, resulting in tendinopathy, inflammation, pain, and sensitivity changes in the lateral elbow. Iontophoresis is a noninvasive method of systemic and local drug delivery by means of a current. The study aimed to evaluate the effects of iontophoresis in patients with LE.
Methods: We performed a randomized, double-blind clinical trial. Twenty-four patients with LE, randomized into an iontophoresis group and a galvanic current group. The iontophoresis group received a solution of dexamethasone (4 mg/mL) and gel lidocaine—applied on the negative electrode by means of a continuous current at 5 mA for 15 minutes—and the positive electrode received a base gel solution. Patients in the galvanic current group received the same protocol but using a base gel solution on both electrodes.
Results: Both groups showed a significant improvement in pain on exertion and rest; increased handgrip strength in elbow extension and flexion; and improved function, as evaluated by the Patient-Rated Tennis Elbow Evaluation scale ($P < .05$). Iontophoresis showed superior results compared with galvanic current in pain on exertion and rest and in the function of individuals with tennis elbow.
Conclusion: Iontophoresis proved to be an effective technique in reducing pain and improving strength and function in individuals with LE (tennis elbow).
Level of evidence: Level I; Randomized Controlled Trial; Treatment Study

Keywords: Iontophoresis; epicondylitis; direct electrical current; tennis elbow; physical therapy; dexamethasone; lidocaine

Lateral epicondylitis (LE), also called tennis elbow or lateral epicondylalgia, is a prevalent arm disorder that affects men and women equally, predominantly between 45 and 54 years of age. Epicondylitis is generally characterized by functional impairment and pain in the epicondyle region and is caused by resisted and repetitive use of the flexor or extensor muscles of the wrist. LE, in turn, is caused by repetitive strain to the extensor tendon, notably the extensor carpi radialis brevis, or by forced extension or direct trauma to the lateral epicondyle. It is the most common cause of elbow and forearm pain in adults, with a prevalence of 1%-3% in the general population.[20] The incidence is 4-7 cases per 1000 patients per year.[19] Despite being commonly referred to as tennis elbow, only 5% of the cases are caused by the practice

The study was approved by the Ethics and Research Committee of the Lutheran University of Brazil (CEP opinion number: 2.152.774).

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of racquet sports.[19] In spite of decades of research investigating its underlying treatments and mechanisms, LE remains a challenging condition for researchers and clinicians.[6] The treatment is generally conservative, consisting of a combination of nonsteroidal anti-inflammatory drugs, orthoses, eccentric contraction-based physiotherapy regimens, or infiltrations.[10] The most prevalent electrophysiological agents in interventions are thermotherapy, transcutaneous electrical nerve stimulation, low-intensity laser therapy, extracorporeal shock wave therapy, ultrasound, phonophoresis, and iontophoresis.[4] Although conservative treatments are often effective, some patients may eventually require surgical intervention.[5] Of the diagnosed cases, 2% require operative treatment.[9] Techniques of open, arthroscopic, or percutaneous surgery have been described in the approach of LE.[10]

Iontophoresis is a type of electrotherapy in which a drug is introduced into tissues by the application of a local electrical current.[14] It is based on the principle that in a given electrical field, positively charged drug ions (cations) are repelled by a positive electrode (anode) and are directed to the cathode (negative electrode).[14] In turn, drugs with negative ions are repelled by the negative electrode (cathode) and are directed to the anode (positive electrode). Iontophoresis uses 2 types of current: direct and alternating.[12] This practice has attracted a great deal of interest in applications of various musculoskeletal disorders such as LE.[22] It is commonly applied through a low-voltage direct current aiming at introducing physiologically active ions topically applied on the body surface.[22] The advantages of iontophoresis include a noninvasive nature, uniform absorption, and absence of systemic side effects such as gastrointestinal discomfort, in addition to being sterile and painless.[22] Among other fields, this method is used in dentistry, ophthalmology, otorhinolaryngology, and dermatology, for the administration of local anesthetics, nonsteroidal anti-inflammatory drugs, antibiotics, anticancer drugs, hormones, and other substances.[7]

Initially, it is important to evaluate the mechanisms of action of direct current. This current produces a sustained direction of electroosmotic transport.[8] The direction of liquid fluid flow can be reversed by altering the polarity of the applied electric field.[8] Cancel et al[8] isolated and quantified the effects of direct current on the endothelial layers that model the blood-brain barrier. With a current of 1 mA for 10 minutes, the authors observed fluid and solute movement with the same stimulation polarity, which persisted only during the stimulation period, suggesting an electroosmotic mechanism. They also showed that the direction of the water flow can be reversed by reversing the direction of the applied current, characteristic of the electroosmotic effect. In addition, the magnitude of the flow induced by direct current was found to be linearly correlated with the magnitude of the applied current.[8] According to Sylvestre et al,[23] the pharmacologic compound used, 4-mg/mL dexamethasone and lidocaine, is negatively charged. Thus, they applied drug gel on the negative electrode, and considering the principle of electroosmotic transport provided by the galvanic current and the principles of applicability of iontophoresis, the composition was administered following its unidirectional course, having a higher concentration in the region of the lateral epicondyle of the elbow.[23]

Manjunatha et al[18] carried out a study with 2.5% and 5% lidocaine in human skin using passive diffusion, alternating current (0.5 mA/cm^2), and direct current (0.5 mA/cm^2). They assessed the permeability of this drug by laboratory analysis using high-performance liquid chromatography. The results showed that lidocaine concentration increased effectively in both currents compared with the passive group. The lidocaine flow was about 6 times higher in alternating current and about 10 times higher in direct current.

Lidocaine is one of the most commonly used topical anesthetic drugs.[15] It temporarily blocks the conduction of free nerve endings in the dermis or mucosa, producing immediate analgesia.[15] The major questions that arise in clinical research are what dose of the drug actually reaches the target tissue and what is the depth of penetration of this drug when using direct current.[15] The origin of the extensor carpi radialis brevis is the most commonly affected structure.[22] This area is very weak.[22] Its structure is located just below the dermis and epidermis layer, with virtually no adipose tissue.[5] For the direct penetration of topical drugs into deep tissues, the drug molecules first need to penetrate through the epidermis and then enter the dermis, where a portion will be carried by the dermal capillary blood flow and the remainder will diffuse into the tissues below the dermis, such as subcutaneous and fascial layers, muscles, or joint tissues.[16] The principle of iontophoresis consists in placing an ionic compound under the electrode according to the polarity, allowing its conduction by an electrical repulsion through the natural barriers of the skin.[11] Gurney et al[11] measured the transmission of dexamethasone sodium phosphate (DEX-P) using iontophoresis. The analysis was performed in the tendon using high-performance liquid chromatography, and iontophoresis proved to facilitate the transmission of dexamethasone to connective tissues in humans, with skin penetration depths up to 30 mm.

Thus, the present study evaluated the effects of iontophoresis in patients with LE in comparison to the galvanic current therapeutic approach. Our hypothesis is that drug administration through iontophoresis presents more satisfactory results in controlling pain and improving strength and function in patients with LE compared to the galvanic current alone.

Materials and methods

Study design

This is a double-blind, randomized clinical trial conducted at the Clinical School of Physiotherapy of the Lutheran University of Brazil (ULBRA) in Torres City, Rio Grande do Sul, Brazil. The study was registered in the Brazilian Registry of Clinical Trials (REBEC-RBR-26gq5n).

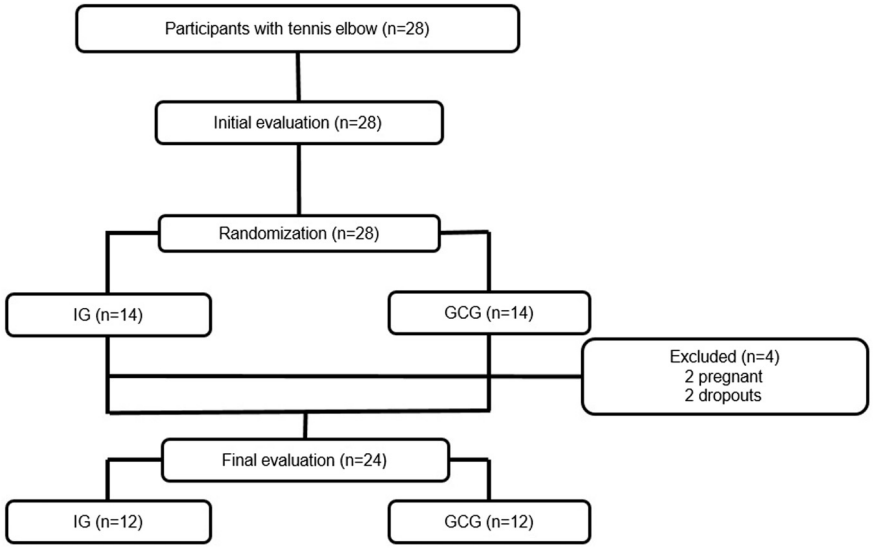

Figure 1 Study flowchart. *IG*, iontophoresis group; *GCG*, galvanic current group.

Sample randomization

Eligible participants were randomized by means of sealed envelopes by an independent researcher, being randomly divided into 2 groups: iontophoresis group (n = 12) and galvanic current group (n = 12). The study participant was not informed about the group he or she belonged to or about which technique was being administered.

Initially, 28 individuals with LE were recruited. Of these, 4 participants were excluded, 2 for being pregnant, not having the medical release for participation in the study, and 2 as a result of withdrawal. All subjects in the iontophoresis group received the prescription of the drug used from a collaborating physician. Therefore, the final sample consisted of 24 individuals (Fig. 1).

Eligibility criteria

The study included participants of both sexes, aged >18 years, who had a clinical diagnosis of LE (uni- or bilateral), who had not received any type of treatment in the last 4 weeks, and who consented and signed the informed consent form.

The following were excluded: individuals with local or generalized arthritis, neurologic deficit, contraindications to the medication to be administered, pain or symptoms of unknown origin, neoplasia diagnosed at the treatment site, or a history of adverse reaction or hypersensitivity to electrical stimulation and those who received some type of conservative treatment for LE in the 4 weeks before the study.

Data collection procedures

The evaluation protocol was performed by a previously trained blinded independent researcher (who did not know the group to which the participant belonged). Evaluations occurred before randomization and after the end of the interventions.

Anthropometric assessment

The body mass index was evaluated by measuring height and body weight. Weight was measured using a previously calibrated anthropometric scale, with the individual wearing light clothing and barefoot. Height was measured using the same scale, through a stadiometer, with the individual barefoot, with arms extended along the body, and in respiratory apnea. Three measurements of height and weight were taken, and their median was recorded.

Pain assessment

A 0-10 visual analog scale (VAS) was used to assess pain, in which 0 indicates no pain and 10 indicates the maximum possible pain.

Muscle strength and handgrip strength assessment

Muscle strength was assessed by hand dynamometry. Handgrip maximum voluntary isometric contraction was measured in kilograms using a Jamar hydraulic hand dynamometer in 2 positions: elbow extended and flexed at 90°. In the first position, the subject was sitting in a chair with his or her arm close to the body, with 90° shoulder flexion in adduction, the elbow in extension, and the forearm in neutral position.

For measuring elbow flexion, the subject was sitting in a chair with his or her arm close to the body, shoulder in adduction, the elbow flexed at 90°, and the forearm in neutral position.

Three measurements of handgrip were taken with a minimum interval of 1 minute, and their median was recorded.

Function assessment

The Patient-Rated Tennis Elbow Evaluation (PRTEE) scale was used to assess function. This questionnaire is validated for the Portuguese language through the study of Andrade et al,[4] consisting

of 15 items to measure pain and disability perceived in people with LE. The questionnaire has 3 subscales: pain, usual activities, and specific activities. The pain subscale has 5 items on pain intensity during various activities. The specific activities subscale has 6 items, addressing the difficulty presented when performing specific activities such as raising a cup of coffee. The 4 items of the usual activities subscale address the difficulty presented in performing usual daily roles such as work and recreation. The final result of the questionnaire is given by the sum of the totals of these subscales.

Iontophoresis and galvanic current intervention protocols

The intervention with direct (galvanic) current and iontophoresis was administered by a previously trained researcher, and occurred 3 times a week for 4 weeks. The subject was blinded to the allocation of the intervention group and was unaware of the treatment he or she was receiving (iontophoresis or galvanic current). The prescription of the solution of 4 mg/mL dexamethasone and 4% lidocaine gel was made by a collaborating physician participating in the study. The subject was seated with his or her arm extended on the examination table. Initially, the skin was properly prepared and sanitized with 70% alcohol to receive the drug. The solution of 4 mg/mL dexamethasone and 4% lidocaine was applied in a volume of 3 mL through a syringe in the negatively charged electrode. The positively charged electrode received a base gel solution. The electrode with the drug was placed directly on the lateral epicondyle of the elbow, and the dispersive electrode was placed distally 10 cm above the belly of the extensor muscles of the wrist. The Endophasys (KLD Biosistemas) electrical stimulator was used, with 5×10-cm rubber electrodes. The initial intensity was 5 mA, and the application time was 15 minutes. If there was a report of irritability to the electrical current, the current intensity was decreased to 3 mA and the time increased to 20 minutes. If the symptom persisted, the procedure would immediately stop. It should be noted that there was no report of discomfort in the sample used.

Individuals in the galvanic current group received the same protocol, but a base gel solution was used on both electrodes.

Depending on the intervention, both groups received a standard program of eccentric exercises and stretches for carpal extensors.

Sample calculation

Handgrip strength, measured by hand dynamometry, was used as a primary endpoint. Based on the study conducted by Stergioulas et al,[22] we estimated the mean and standard deviation (SD) of the initial handgrip strength of the study participants at 24.81 ± 2.29 kg in the iontophoresis group and 25.98 ± 2.23 kg in the galvanic current group, and the final (pain-free) handgrip strength after 6 weeks of treatment at 31.63 ± 3.17 in the iontophoresis group and 26.15 ± 2.31 kg in the galvanic current group. Considering a study power of 80%, a significance level of 95%, and a sample size ratio of 1:1 (iontophoresis group–galvanic current group), we reached the estimated number of 12 subjects for each group, totaling 24 subjects.

Statistical analysis

The Statistical Package for the Social Sciences, version 17.0 (IBM, Armonk, NY), was used for data analysis. Initially, a descriptive analysis of the study variables was performed using absolute number, frequency, and mean and SD. Afterward, data distribution normality was assessed using the Shapiro-Wilk test. Finally, parametric data were statistically analyzed by paired Student *t* test for intragroup comparisons and by unpaired Student *t* test for intergroup comparisons. For nonparametric variables, we used the Wilcoxon tests within each group and the Mann-Whitney tests for intergroup comparisons. The significance level established for the statistical test was $P < .05$.

Results

The study had a total sample of 24 participants randomly assigned to the iontophoresis group (n = 12) and galvanic current group (n = 12). Table I shows the initial characteristics of the sample. The groups were homogeneous regarding the analyzed variables.

There was a significant reduction in pain at rest in both intervention groups ($P < .05$). However, at the end of the study, the iontophoresis group showed a significantly lower pain level than the galvanic current group ($P = .002$) (Fig. 2). The mean (±SD) pain level in the galvanic current group reduced from 3.50 ± 2.11 to 2.50 ± 1.57 ($P = .032$), whereas in the iontophoresis group, it reduced from 3.83 ± 1.80 to 0.58 ± 0.99 ($P = .000$) (Fig. 2).

Pain on exertion also decreased significantly in both intervention groups ($P < .05$). However, at the end of the study, the iontophoresis group again showed a significantly lower pain level than the galvanic current group ($P = .000$) (Fig. 3). The mean (±SD) pain level in the galvanic current group reduced from 8.17 ± 2.17 to 4.92 ± 1.93 ($P = .000$), whereas in the iontophoresis group, it reduced pain from 8.33 ± 1.44 to 1.83 ± 1.75 ($P = .000$) (Fig. 3).

Muscle strength, represented by maximum voluntary isometric contraction, increased significantly in the groups after the intervention ($P < .001$). Notwithstanding, no differences were observed between the groups (Table II).

The functional level, assessed through the PRTEE questionnaire, increased in both intervention groups. The PRTEE score reduced in the iontophoresis group both in the pain subscale and in function, with a total score significantly higher than that of the galvanic current group ($P < .000$) (Table III).

Discussion

In the present study, we investigated the effect of iontophoresis on pain reduction, functionality, and handgrip strength in individuals with LE. The high incidence of tendinous lesions in the population and the failure rate of up to 25% in conservative treatments available for this type of lesions have made this field one of the most interesting for alternative biological approaches.[17] However, multiple randomized controlled trials for nonsurgical management of LE do not provide conclusive evidence that there is one

Table I Characteristics of the study sample (n = 24)

Variable	Intervention group		*P* value
	Iontophoresis (n = 12)	Galvanic current (n = 12)	
Age, yr*	49.75 ± 8.09	50.25 ± 10.19	.895
Gender, M/F, n†	5/7	5/7	1.000
Affected arm, n (%)†			1.000
Right	9 (75.0)	9 (75.0)	
Left	3 (25.0)	3 (25.0)	
Skin color, n (%)†			1.000
White	12 (100.0)	12 (100.0)	
Black	0 (0.0)	0 (0.0)	
Weight, kg*	70.40 ± 8.21	75.75 ± 16.51	.330
Height, cm*	166.58 ± 6.08	166.33 ± 6.34	.922
BMI*	25.31 ± 2.77	27.24 ± 5.22	.275

SD, standard deviation; *M*, male; *F*, female; *BMI*, body mass index.
Values are mean ± standard deviation unless otherwise noted.
* Student *t* test.
† Chi-square test.

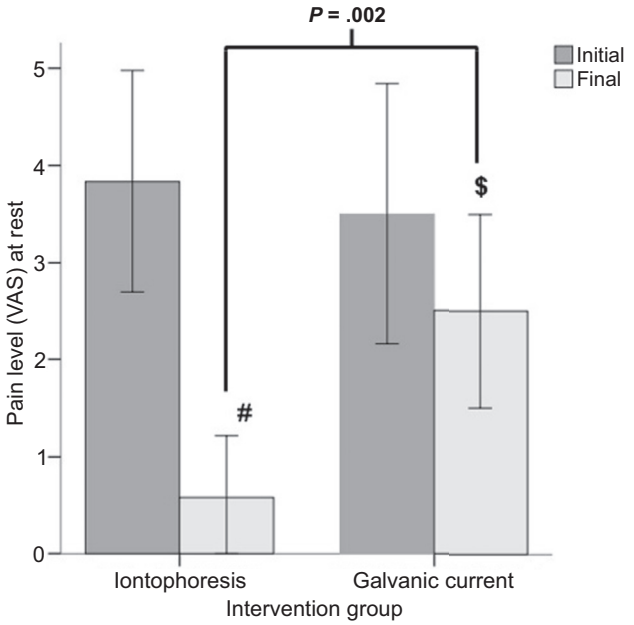

Figure 2 Assessment of pain at rest (VAS score) in study groups. #$P = .0001$ in relation to the initial evaluation of the same group. Student *t* test. $$P = .013$$ in relation to the initial evaluation of the same group (Student *t* test). *VAS*, visual analog scale.

preferred method of nonsurgical treatment for this condition.[21]

Historically, tendinopathy had been considered a degenerative pathologic process of a noninflammatory nature, because the presence of inflammatory cells in chronic tendinopathy had not been confirmed.[1] However, thanks to

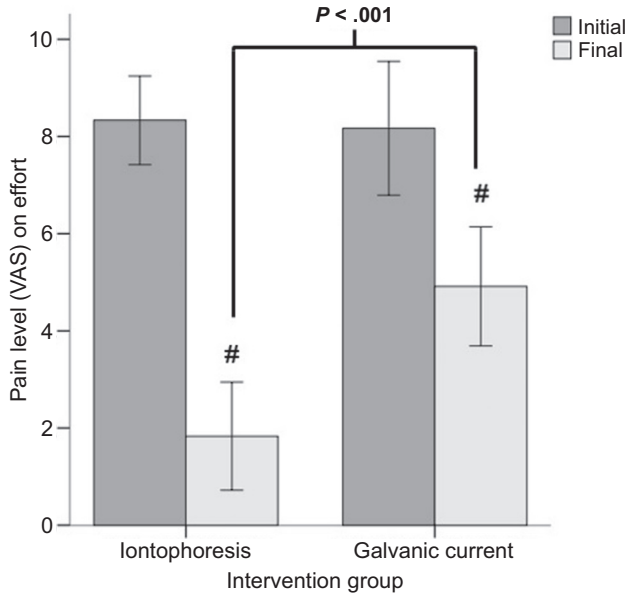

Figure 3 Assessment of pain on exertion (VAS score) in study groups. #$P = .0001$ in relation to the initial evaluation of the same group (Student *t* test). *VAS*, visual analog scale.

the new research instruments, convincing evidence demonstrates an increasing number of inflammatory cells in pathologic tendons, showing that the inflammatory response is a key component also present in chronic tendinopathy.[1,9]

Pain intensity at rest and on exertion decreased significantly in both intervention groups. The iontophoresis group demonstrated a significantly lower final pain level than the galvanic current group. Corroborating these findings, Stergioulas et al[22] investigated the effect of iontophoresis with the administration of 4 mg/mL dexamethasone and 4% lidocaine in 85 patients with LE randomized to an iontophoresis group (n = 43) and a placebo group (n = 42). Pain intensity, handgrip strength, and function were assessed. In the iontophoresis group, pain intensity decreased significantly at the end of the treatment, and there was an increase in both handgrip strength and function. In contrast, there were no significant changes for the placebo group, leading the authors to conclude that iontophoresis using this pharmacologic composition had significant effects.[3] Akhondali et al[2] demonstrated that iontophoresis reduced pain levels in the same manner as the Cyriax technique in 22 subjects with lateral elbow epicondylitis.

Sylvestre et al[23] evaluated the effects of ions and electroosmosis on iontophoresis with DEX-P and identified the best conditions for its administration. The experiments were performed with pig skin, using a constant current of 0.3 mA. DEX-P transport was analyzed for administration polarities (anodic and cathodic), different concentrations of drugs with and without electrolytes, Na^+ and K^+ levels,

Table II Maximum voluntary isometric contraction of initial and final grip strength in study groups (n = 24)

Grip strength (kg)	Group	Baseline, mean ± SD	Post-treatment, mean ± SD	*P* value*	Effect size	Intragroup variation (95% CI)	*F*	*P* value†
Extended elbow	Iontophoresis	28.17 ± 11.84	36.25 ± 11.39	**.001**	−4.77	−8.08 (−11.81, −4.35)	0.809	.194
	Galvanic current	20.67 ± 9.88	30.17 ± 10.84	**.002**	−4.02	−9.50 (−14.70, −4.30)		
Flexed elbow	Iontophoresis	27.83 ± 7.87	34.00 ± 9.14	**.001**	−4.60	−6.17 (−9.12, −3.21)	0.741	.517
	Galvanic current	20.33 ± 9.53	31.08 ± 12.27	**.007**	−3.30	−10.75 (−17.92, −3.58)		

SD, standard deviation; *CI*, confidence interval.
Bold values are statistically significant.
* Student *t* test for intragroup comparisons.
† Student *t* test for intergroup comparisons.

Table III Evaluation of the initial and final PRTEE Questionnaire scores in the study groups (n = 24)

PRTEE	Group	Baseline, mean ± SD	Post-treatment, mean ± SD	*P* value*	Effect size	Intragroup variation (95% CI)	*F*	*P* value†
PRTEE pain	Iontophoresis	31.83 ± 3.13	9.00 ± 5.89	**.000**	12.16	22.3 (18.70, 26.97)	0.387	**.000**
	Galvanic current	33.33 ± 7.19	20.33 ± 7.16	**.000**	5.37	13.00 (7.67, 18.32)		
PRTEE function	Iontophoresis	36.35 ± 6.64	10.33 ± 7.73	**.000**	9.33	25.92 (19.80, 32.03)	0.022	**.000**
	Galvanic current	38.33 ± 7.44	26.13 ± 8.76	**.005**	3.48	12.21 (4.48, 19.93)		
PRTEE total	Iontophoresis	68.08 ± 7.86	19.33 ± 12.62	**.000**	11.12	48.75 (39.10, 58.40)	0.067	**.000**
	Galvanic current	71.67 ± 13.35	46.46 ± 14.95	**.001**	4.52	25.21 (12.94, 37.48)		

PRTEE, Patient-Rated Tennis Elbow Evaluation; *SD*, standard deviation; *CI*, confidence interval.
Bold values are statistically significant.
* Student *t* test for intragroup comparisons.
† Student *t* test for intergroup comparisons.

and the contribution of electroosmosis. The authors concluded that the administration of DEX-P through the anode (positive electrode) was inefficient and therefore should be avoided. Finally, they concluded that the pharmacologic mixture of dexamethasone phosphate and lidocaine hydrochloride presented better results compared with the other groups, being better administered in a current intensity of 0.3-0.5 mA/cm^2 for up to 20 minutes, with a composition of 0.4% dexamethasone and 4% lidocaine applied on the negative electrode, similar to that used in the current study.[23]

The present study demonstrated significant results on function (ie, PRTEE score) in both intervention groups. However, the final results of those in the iontophoresis group showed a significantly higher level of functionality compared to the group that administered only the galvanic current. Altan et al[3] tested the reliability of the PRTEE by correlating and comparing their results with the DASH and QDASH scales. The study included 50 patients (14 men and 36 women) diagnosed with LE. The subscale pain, function, and the general score of PRTEE showed significant correlations with the DASH and QDASH scales, demonstrating that the PRTEE scale is valid and reliable.

Both intervention groups in our study significantly improved handgrip strength, at elbow extension as well as flexion. Baktir et al[5] compared the efficacy of low-level laser therapy, phonophoresis with topical prednisolone (2 mg/d), and iontophoresis with current intensity in the range of 3-5 mA/min and total dose of 40 mA, with a solution of 5 mL of 0.4% prednisolone, in 37 patients with LE. Fifteen sessions were administered to all groups. Pain level was evaluated using a visual analog scale, handgrip strength through a hand dynamometer, and functionality through the PRTEE scale. The authors concluded that iontophoresis showed better results for pain, function, and handgrip strength. Functional improvement included muscle grip strength, which was also evaluated in several studies, many of them using the PRTEE score.[5] This score is a specific evaluation for LE.[5]

Kalra[13] analyzed the efficacy of Iontophoresis with 4 mg/mL dexamethasone and 4% lidocaine hydrochloride in 40 patients diagnosed with plantar fasciitis. A direct current of 4 mA/min was applied for 10 minutes (total dose of 40 mA) on the negative electrode, 3 times a week, for 2 weeks.[13] The dosimetry was similar to that used in our study. The author concluded that iontophoresis with dexamethasone and lidocaine hydrochloride was effective in the treatment of plantar fasciitis.

Study limitations

This study has some limitations that should be highlighted. First is the relatively small sample size. Second, the results do not reflect a long-term therapeutic reality, that is, the results were evaluated only shortly after the end of the intervention. A third important aspect is that it is not possible to accurately quantify the drug dose that reached the target tissue, that is, the insertion of the extensors at the level of the lateral epicondyle. Thus, we suggest further studies be conducted addressing these conditions.

Conclusion

Iontophoresis proved to be an effective technique in reducing pain and improving strength and function in individuals with LE.

Disclaimer

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