A Systematic Review on the Efficacy of Iontophoresis as a Treatment for Lateral Epicondylitis

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Abstract

Background and purpose: It is still inconclusive which method of iontophoresis delivers the most medication deepest through the skin, and therefore most effective in treating lateral epicondylitis. The purpose of this systematic review is to analyze the efficacy of treatments for lateral epicondylitis using iontophoresis.

Method: The review included articles from peer-reviewed journals with sufficient data related to the purpose and focus of the study. Inclusion criteria included randomized control trials, cohort studies, case studies, systematic reviews, meta-analyses, and pilot studies published since 2000.

Results: Fourteen relevant studies were identified. Twelve were experimental in vivo studies, two were review studies. All studies were published 2002 through 2015, providing a robust overview of treatments over the last 15 years.

Discussion and conclusion: Among studies in this systemic review, pooled data from RCTs pointed to minimal intermediate- to long-term clinical benefit for the nonsurgical treatment of lateral epicondylitis. Of drug treatments, the most frequently used in iontophoresis are dexamethasone and lidocaine. Studies of iontophoresis with dexamethasone show evidence that the combination of treatments may be effective in reducing pain; there is evidence supporting the iontophoretic administration of dexamethasone as an alternative to other medication and oral therapy. Based on this review, it is not conclusive that iontophoresis be recommended as a treatment approach for the management of epicondylitis, however iontophoresis should not be ruled out in treating epicondylitis as it is a dose-response modality. More research and review of research is needed on the use of iontophoresis in managing epicondylitis.

Keywords: Iontophoresis; Lateral epicondylitis; Drug-delivery; Transcutaneous; Tendinopathy

Introduction

Lateral epicondylitis, or tennis elbow, is a painful condition typically caused by overuse of the tendons, resulting in tendinopathy, inflammation, pain, and tenderness to the lateral elbow. The condition involves the extensor carpi radialis brevis, part of the wrist extensor musculature. These extensor muscles of the forearm help stabilize the wrist to create a useful and powerful grip of the hand. As many as 15% of workers making highly repetitive motions with their hands contract this condition and on average lose up to 12 weeks of work [1]. Several treatments for lateral epicondylitis exist. One treatment is iontophoresis, a technique that delivers a medicine through the skin using electrical current, also called transdermal delivery. This technique enhances the absorption of drugs across biological tissue such as skin. Traditionally, iontophoresis involves a machine utilizing direct current with lead wires. Using a dosage up to 5mA a treatment would last between 16 minutes and 30 minutes. Currently, clinicians use iontophoresis as an adjunct intervention treatment for lateral epicondylitis, as well as other conditions.

Many advances in iontophoresis have occurred since then. Advances in newer technologies have also occurred. Recently, therapists have been using a self-contained patch that relies on no wires. The patch uses a very low current, less than 1mA, to deliver the medication over a span of up to 14 hours. However, there is not much research to date on its effectiveness compared to traditional iontophoresis. Other forms of treatment also exist, including Lidocaine and Dexamethasone. Lidocaine is within the category of drugs that includes local anesthetics. The drug is administered topically using a transdermal patch and a low-grade electrical current from an iontophoresis unit [2]. The main benefit of lidocaine is that it admits analgesic effects to a particular area of the body so that treatment can occur with less pain [3]. The other common drug treatment for epicondylitis is Dexamethasone, a synthetic derivative of glucocorticoid steroid that is 25 times more efficient in reducing inflammation, with little retention of sodium [2]. The glucocorticoids inhibit the release of inflammatory proteins; however the method by which the glucocorticoids attenuate heat, swelling, erythema, and tenderness is not completely understood. Overall, the results with dexamethasone have been found to be remarkable.

It is known that medications can be very effective when treating soft tissue injuries, but often injections are the primary method...
by medical doctors for such conditions. Iontophoresis is the most common non-invasive treatment using medications. A few studies have been conducted on iontophoresis; however most have been on the effects of different medications. Many studies have also looked at the effectiveness of a particular medication for lateral epicondylitis. When using iontophoresis, it is still inconclusive which method can deliver the most medication deepest through the skin, and which drug provides the most efficient treatment of lateral epicondylitis. By learning the best method and medications to treat lateral epicondylitis, physical therapists can provide individuals with this debilitating disorder greater improvement and outcomes of movement. The purpose of this systematic review is to provide physical therapy clinicians with pertinent information regarding progression of lateral epicondylitis treatment using iontophoresis and to analyze the evidence for the efficacy of the method in physical therapy.

Methods

The following databases were searched for relevant articles: PubMed, Cochrane Library, PEDro, SPORT Discus, Google Scholar, and the APTA library. Key words consistently used during the search were “lateral epicondylitis,” “epicondylitis,” “epicondylalgia,” “iontophoresis,” “trans-dermal,” “effectiveness,” “dexamethasone,” “lidocaine,” and “physical therapy.” Abstracts of all the articles retrieved were reviewed to determine relevancy. Full peer-reviewed articles that fit the inclusion criteria were retrieved. In addition, a manual search was conducted of references within relevant articles and obtained for a full assessment.

Eligibility criteria

This systematic review included articles found in peer-reviewed journals with sufficient data related to the purpose and focus of the study. The inclusion criteria included randomized control trials, cohort studies, and case studies, systematic reviews, meta-analyses, and pilot studies. Extensive findings were narrowed down to a core of relevant literature published since 2000. Articles published before 2000 were excluded during the search, however were kept for any relevant background information. Also excluded were articles published in languages other than English that did not have an English version published. Additional exclusion criteria included retrospective studies, case studies, lack of study design description or had no full text available.

Critical appraisal

Two types of critical appraisal strategies were used for this study: the Physiotherapy Evidence Database (PEDro) scale and the AMSTAR scale. The PEDro scale was used to assess the quality of each randomized controlled trials (RCT). The AMSTAR scale was used to assess the quality of both a meta-analysis and a systematic review.

Data Extraction and Analysis

All relevant articles that met the inclusion criteria were prepared for assessment using a data extraction form. All literature has data extracted using the Cochrane data extraction sheet for systematic reviews. The data sheet helped in the correlation and comparison of necessary information including but not limited to the type of intervention, blinding of subjects, outcomes, method of subject selection, and comparison of experimental and control groups. The information from these forms was assessed for quality and validation of all obtained articles. The PEDro scale was used to evaluate the quality of each RCT. For studies retrieved from the Pedro database, the Pedro scores provided were accepted. The Pedro rating tool comprised eleven items. Items where criteria were fulfilled were scored with a “*,” a “−” if the criteria were not fulfilled, and “?” if the provided information was unclear and considered “not fulfilled.

The items rated are as follows:

1) Eligibility criteria were specified,
2) Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated to an order in which treatments were received),
3) Allocation was concealed,
4) The groups were similar at baseline regarding the most important prognostic indicators,
5) There was blinding of all subjects,
6) There was blinding of all therapists who administered the therapy,
7) There was blinding of all assessors who measured at least one key outcome,
8) Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups,
9) All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analyzed by “intention to treat,”
10) The results of between-group statistical comparisons are reported for at least one key outcome, and
11) The study provides both point measures and measures of variability for at least one key outcome [4].

Additionally, the quality of all studies were assessed using the Oxford Centre for Evidence-based Medicine Levels of Evidence, which grades the quality of research and includes five levels of recommendations:

(A) Consistent level 1 studies (very good quality)
(B) Consistent level 2 studies or extrapolations from level 1 studies (good quality)
(C) Consistent level 3 studies or extrapolations from level 2 studies (moderate quality)
(D) Level 4 studies or extrapolations from level 2 or 3 studies (low quality)
(E) Level 5 evidence or troublingly inconsistent or inconclusive studies of any level (very low quality)

Results
Selection of studies
The database search yielded to 48 possibly eligible studies. After reviewing titles and abstracts, the search was reduced to 16 studies. Two papers were excluded because one did not meet criteria and one was a duplicate that had not yet been removed. Among the resulting 14 relevant studies, 12 were experimental in vivo studies, while two were review studies. The latter is used within the discussion section only. All the papers were published in medical journals, two of them in the Journal of Orthopedic & Sports Physical Therapy [5] and the rest of different prestigious journals. The publication years were all 2002 and later; one study was published in 2002, three in 2003, one each in 2006, 2008, 2011, and 2012, and three in 2015, giving a robust overview of the treatment and review of the problem over the last 15 years.

Methodological quality
The quality of the study designs ranged from Pedro scores of 3 to 11 out of 11. Studies with a Pedro score of 7 and above were rated “high,” those with a Pedro score of 5 or 6 were rated as “moderate,” and those with a Pedro score of 4 or below were rated as low-quality studies. The mean Pedro score for the 11 studies reporting positive effects of iontophoresis treatment was 6.27±2.52 SD, while one study with a negative treatment outcome had a Pedro score of 8, indicating a moderate quality of research in this topic area. Patient randomization was done in seven of the studies, indicative of a good-quality research paper. Blinding was the most lacking in the Pedro score; due to the nature of the interventions, it is not possible for patients or care providers to be blinded. Patient blinding, care provider blinding, and outcome assessment blinding was done in only three studies [5-7]. Patient allocation was most often judged as unclear and has a low Pedro score review. These items were therefore considered unacceptable, especially blinding.

The Oxford Centre for Evidence-based Medicine Levels of Evidence was used to assess evidence. Two studies were found with a reported level 1b [6,8]. One study reported level 2a (good quality [9]). Five studies were reported level 2b (good quality [5,7]). Two studies were reported level 3b (moderate quality; Draper et al. [3]), and two were reported level 4 (low quality [5,10]).

Discussion
The purpose of this systematic review is to provide physical therapy clinicians with pertinent information regarding progression of lateral epicondylitis treatment using iontophoresis and to analyze evidence for the efficacy of the method in physical therapy. After searching databases in combination with reference checking for randomized controlled clinical trials, a total of 12 studies were analyzed. All 12 studies report the effectiveness of iontophoresis in the management of epicondylitis and are displayed in the table below Table 1.

Table 1: Descriptive characteristics of the included studies assessing treatments of lateral epicondylalgia.

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Study Design</th>
<th>Participants</th>
<th>Diagnosis</th>
<th>Treatment Frequency</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stefanou et al. [9]</td>
<td>Randomized</td>
<td>82 patients</td>
<td>lateral</td>
<td></td>
<td>Group 1: 10mg of dexamethasone via iontophoresis using self-contained patch with a 24-hour battery (n=31); Group 2: 10mg dexamethasone injection (n=27); Group 3: 10mg triamcinolone injection (n=28).</td>
<td>delivery of dexamethasone compared to corticosteroid injection therapy in patient outcomes</td>
<td>Change in grip strength (flexion vs. extension), pain, function scores on a validated questionnaire; secondary outcome was return-to-work status; evaluated at baseline, completion of physical therapy, and 6-month follow-up.</td>
<td>Group 1: statistically significant improvement in grip strength at the end of hand therapy (20±4) compared with baseline (1±4a) (p&lt;0.01); statistically significant improvement in the outcome of pain at the end of the therapy (7.2±2.7) compared to the baseline (5.7±1.8) (p&lt;0.05). At six-month follow-up, all groups had equal results for all measured outcomes.</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Intervention</td>
<td>Outcome Measures</td>
<td>Summary</td>
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<td>Nirschl et al. [6]</td>
<td>double-blinded randomized placebo-controlled</td>
<td>199</td>
<td>6 treatments, over 15 days, 1-3 days apart</td>
<td>40 mA-minutes of either active (n=99) or placebo treatment (n=100) transdermal administration of dexamethasone sodium phosphate</td>
<td>Reduced symptoms of medial or lateral epicondyritis with significant pain reduction for the patients (p&lt;0.05); significant 2.3mm improvement on the 100mm patient visual analog scale ratings.</td>
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<td>Wen et al. [8]</td>
<td>RCT</td>
<td>28 adults</td>
<td>chronic lateral epicondylitis</td>
<td>Experimental group: 3 sets of 15 repetitions daily, met with the therapist twice a week for the first 2 weeks, then once per week for 12 weeks; control group: same schedule as experimental group</td>
<td>Overall satisfaction and grip strength showed no statistically significant differences between the groups. For the control group, a statistically significant decrease of 28 points occurred between baseline and the four-week follow-up with P&lt;0.01. Secondary outcomes indicated a statistically significant improvement in pain level compared with baseline favoring the eccentric strengthening group at the eight-week time point.</td>
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<tr>
<td>Runeson et al. [7]</td>
<td>RCT and double-blinded study</td>
<td>64</td>
<td>lateral epicondylalgia</td>
<td>Four times over 2 weeks corticosteroid or placebo</td>
<td>Subjective and objective outcomes of pain and grip strength; evaluated day after final treatment and after 3 and 6 months Differing results from other papers, showing no significant difference in pain relief between the corticosteroid group (n=33) and the placebo group (n=31).</td>
<td></td>
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<tr>
<td>Authors/Glenn</td>
<td>Study Design</td>
<td>N</td>
<td>Diagnosis</td>
<td>Treatment</td>
<td>Clinical Improvement</td>
<td>Drug Delivery Methodology</td>
<td>Conclusion</td>
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<tr>
<td>Yarrobino et al. [3]</td>
<td>Case series</td>
<td>5</td>
<td>Epicondylalgia</td>
<td>Every-other-day basis for a total of three treatment sessions, cryotherapy, cross-fiber massage, and passive stretching.</td>
<td>Lidocaine iontophoresis-mediated analgesia in a bigger treatment algorithm</td>
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<tr>
<td>Draper et al.</td>
<td></td>
<td>10</td>
<td>Lateral humeral epicondylalgia; epicondylitis</td>
<td>Administered iontophoresis at 40mA/min using 2mL of 2% lidocaine.</td>
<td>Whether iontophoresis could deliver lidocaine with epinephrine 5 mm under the surface of human skin as measured by microdialysis.</td>
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<tr>
<td>Anderson et al. [10]</td>
<td>Experiment</td>
<td>5</td>
<td>Healthy adults</td>
<td>In vitro cathodic iontophoresis at 4mA and 0.1mA each delivered dexamethasone/dexamethasone phosphate from a 4mg/mL donor solution to a depth of 12mm following a 40mA minute stimulation dosage.</td>
<td>Iontophoretic doses delivered at low currents over several hours are more effective than those delivered by higher currents over 10-30 minutes in the formation of a localized physiologic effect for DEX/DEX-P.</td>
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5/10
<table>
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<tr>
<th>Study Description</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al. [10]</td>
<td>experiment</td>
<td>Healthy adults</td>
<td>5</td>
<td>80-mA-minute drug delivery had been administered, the in vivo iontophoretic delivery was measured at 1.40 +/- 0.23mg, while the corresponding passive delivery was 0.26 +/- 0.16mg. The in vitro experiments confirmed iontophoretic delivery of dexamethasone phosphate across artificial membranes, and the in vivo experiments suggested that the drug was delivered to the human skin.</td>
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<tr>
<td>Brickman et al. (2015)</td>
<td>Randomized control design</td>
<td>39 patients</td>
<td>acute soft tissue injuries</td>
<td>80-mA-minute drug delivery had been administered, the in vivo iontophoretic delivery was measured at 1.40 +/- 0.23mg, while the corresponding passive delivery was 0.26 +/- 0.16mg. The in vitro experiments confirmed iontophoretic delivery of dexamethasone phosphate across artificial membranes, and the in vivo experiments suggested that the drug was delivered to the human skin.</td>
<td>Efficacy of iontophoresis utilizing a transcutaneous process to transport charged medication to a localized area of soft tissue injury via an electrical current</td>
</tr>
<tr>
<td>Gurney et al. [5]</td>
<td>Experimental lab study</td>
<td>16 adults (10 male, 6 females; mean age 33 years old)</td>
<td>Undergoing anterior cruciate ligament reconstruction</td>
<td>Tendon slip was extracted within four hours</td>
<td>A 40mA/min dose of iontophoresis with 0.4% DEX-P superficial to a small piece of the distal semitendinosus tendon before surgery</td>
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Seven had measurable amounts of DEX-P in the tendon slip; average concentration of the tendon tissue in the 16 subjects was 2.9ng/g. No correlation existed between DEX-P absorbed and skinfold thickness ($r = -0.08, P = .79$) or the time elapsed ($r = 0.25, P = .38$). Among the seven individuals who showed measurable levels of DEX-P absorbed, the average concentration of DEX-P was 6.6mg/g. There was a relationship between DEX-P concentrations and time elapsed, however not statistically significant ($r = 0.71, P = .11$). Iontophoresis appeared to facilitate the transmission of dexamethasone to connective tissues with skin fold thickness up to at least 30mm in humans and the absorption of the dexamethasone appeared to continue occurring up to four hours after delivery.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Results</th>
</tr>
</thead>
</table>
| Gurney et al. [5] | Randomized | 29 | In the true iontophoresis group (n=16), a 40mA/min dose of iontophoresis using a 0.4% (4mg/mL) solution of dexamethasone was utilized to target the semitendinosus tendon just before surgery. The sham iontophoresis group (n=13) underwent the same treatment, but with the machine off.
Statistically significant dexamethasone concentration difference between groups (P=.0216); in the TI group, eight had measurable amounts of dexamethasone, averaging a concentration of 2.906mg/g of tendon tissue. In the SI group, one of the 13 samples had measurable amounts of dexamethasone, averaging a concentration of 0.205 mg/g of tendon tissue. Dexamethasone was not found in the control group. Also shown was a significantly higher proportion of patients receiving true iontophoresis had detectable levels of dexamethasone in their connective tissues than those receiving a sham treatment. Results suggested that iontophoresis using dexamethasone should be considered as part of the management of acute inflammatory conditions. |
<table>
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<tr>
<th>Study</th>
<th>Random assignment</th>
<th>64</th>
<th>healthy men</th>
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<tr>
<td>Rigby et al. (2015)</td>
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Four groups compared different mA currents with different probe depths, and two others underwent vivoretdialysis and skin perfusion flowmetry.

Time course of dexamethasone sodium phosphate to underlying tissues using micro dialysis during iontophoresis.

Microdialysis probes were used to measure the combined recovery (DEX-total) of DEX-P, dexamethasone, and its metabolite.

No difference in DEX-total between current intensities (P = .99), but a larger amount of DEX-total was recovered superficially at 1 mm versus the 4 mm depth (P < .0001). Skin perfusion returned to baseline levels earlier during 1-mA intensity at a 110 mA-min dose within the treatment versus the 2 mA at 60 minutes post-treatment. Based on this study, DEX-P iontophoresis is effective at clinically relevant delivery concentrations of DEX-total to superficial tendons. DEX-total recovery increased throughout the iontophoresis treatment at similar rates between the 1 and 2 mA current intensities, indicating no difference in drug delivery between our high- and low-current intensities up to a total dose of 120 mA/min.

Among studies in this systemic review, those of iontophoresis with dexamethasone show plenty of evidence that the combination of treatments may be effective in reducing pain and that there is insufficient evidence supporting the use of corticosteroid iontophoresis. However, the systematic review of Sayegh & Strauch [11] regarding the effectiveness of physical interventions for lateral epicondylalgia reported contradictions in the results and heterogeneity of the interventions. Additionally, how the drugs intervene with iontophoresis was not considered making it difficult to draw conclusions about the treatment [12-16]. Pooled data from the RCTs point at a lack of intermediate to long-term clinical benefit for the nonsurgical treatment of lateral epicondylitis compared with observation only or placebo.

Of drug treatments, the most frequently used in iontophoresis are dexamethasone and lidocaine. There is evidence supporting the iontophoretic administration of dexamethasone as an alternative to other medication and oral therapy. The current-assisted transdermal delivery of the drug is a non-invasive and safe method, has demonstrated low incidence of side effects, and is a well-tolerated therapy. Additionally, studies concerning treatment for epicondylitis using lidocaine reported promising results [16-21]. However, Pedro scores showing lack of quality of these studies as
Conclusion
Evidence was sought related to the clinical effectiveness of iontophoresis in epicondylitis. A sufficient number of studies were considered for this systematic review. All except one study showed good results for the effectiveness of iontophoresis in epicondylitis. However, based on this evidence, it is not conclusive that iontophoresis should be recommended as a treatment approach for the management of epicondylitis. Results of this review mostly contradict those of Dimitrios et al. [27] that iontophoresis should not be ruled out in treating epicondylitis as it is a dose-response modality, the best treatment dose has not yet been discovered. Therefore more research and review of research is needed on the use of iontophoresis in managing epicondylitis.

References