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

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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.

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 [9], five studies were reported level 2b [5,7], two studies were reported level 3b [9], two two were reported level 3b [9], and two were reported level 4 [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>
<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>Group 1=24 hour battery; Group 2=single injection; Group 3: single</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>
</tbody>
</table>

**Table 1:** Descriptive characteristics of the included studies assessing treatments of lateral epicondylalgia.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Treatment</th>
<th>Transdermal Administration</th>
<th>Pain Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nirschl et al. [6]</td>
<td>Double-blinded randomized placebo-controlled</td>
<td>199</td>
<td>Iontophoresis (2 mL of 4% dexamethasone sodium phosphate) 40 mA-minutes of either active (n=99) or placebo treatment (n=100)</td>
<td>(p&lt;0.05); significant 23mm improvement on the 100mm patient visual analog scale ratings.</td>
<td></td>
</tr>
<tr>
<td>Wen et al. [8]</td>
<td>RCT</td>
<td>28 adults</td>
<td>Eccentric strengthening program against a wrist extensor stretching/modality program</td>
<td>(n=14) of eccentric strengthening group and the control group (n=14) local modality treatments and iontophoresis (2mL of 4% dexamethasone with a 40mA/min).</td>
<td>Reduced symptoms of medial or lateral epicondylitis with significant pain reduction for the patients (p&lt;0.05); significant 23mm improvement on the 100mm patient visual analog scale ratings.</td>
</tr>
<tr>
<td>Runeson et al. [7]</td>
<td>RCT and double-blinded study</td>
<td>64</td>
<td>Iontophoresis of dexamethasone phosphate short- and long-term pain-relieving effect of dexamethasone iontophoresis versus placebo iontophoresis</td>
<td>Subjective and objective outcomes of pain and grip strength; evaluated day after final treatment and after 3 and 6 months</td>
<td>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>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>N</td>
<td>Condition</td>
<td>Intervention</td>
<td>Clinical outcomes</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>-----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<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>
</tr>
<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 4mg/mL donor solution to a depth of 12mm following a 40mA minute stimulation dosage</td>
<td>Vasoconstriction lasted longer and was greater in magnitude when using low current, long-duration (~0.1mA) iontophoresis versus equivalent dosages delivered by higher-current, shorter-duration (1.5–4.0mA) iontophoresis. Based on the duration and magnitude of local cutaneous vasoconstriction.</td>
</tr>
<tr>
<td>Anderson et al. [10]</td>
<td>Experiment</td>
<td>5</td>
<td>Healthy adults</td>
<td>Vitro evaluations of dexamethasone phosphate iontophoresis and in vivo estimations of drug amounts (milligrams) provided via iontophoresis</td>
<td>Optimal parameters required for the clinical iontophoresis of dexamethasone phosphate. After an 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>
</tr>
<tr>
<td>Brickman et al. (2015)</td>
<td>Randomized control design</td>
<td>39 patients</td>
<td>Acute soft tissue injuries</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>
<td>Comparing iontophoresis treatment with using lidocaine and dexamethasone (n=21) to a control NSAID group (n=18). Level of pain at the initiation of treatment, average pain scores for the treatment and control groups were 7.29 and 6.50, respectively. At 30 minutes post-treatment, a greater reduction in pain (62%) was seen in the iontophoresis group compared reduction in the control group (8%) (p&lt;0.001).</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 semitendinosis tendon before surgery</td>
</tr>
<tr>
<td>Gurney et al. [5]</td>
<td>randomized</td>
<td>29</td>
<td>In the true iontophoresis group (n=16), a 40mA/ min dose of iontophoresis 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. True iontophoresis and sham iontophoresis; facilitation of dexamethasone absorption in connective tissue compared with diffusion.</td>
<td>Statistically significant dexamethasone concentration difference between groups (P=0.0216); 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, there 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.</td>
<td></td>
</tr>
</tbody>
</table>
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 systemic 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] 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