A Randomized Study Comparing Corticosteroid Injection to Corticosteroid Iontophoresis for Lateral Epicondylitis

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Purpose We designed a prospective, randomized study to evaluate the effects of iontophoresis delivery of dexamethasone versus corticosteroid injection therapy on patient outcomes.

Methods We randomized 82 patients to 10 mg dexamethasone via iontophoresis using a self-contained patch with a 24-hour battery; 10 mg dexamethasone injection; or 10 mg triamcinolone injection. All patients received the same hand therapy protocol. Primary outcomes tracked were change in grip strength (flexion vs extension), pain, and function scores on a validated questionnaire. The secondary outcome was return-to-work status. Patients were evaluated at baseline, completion of physical therapy, and 6-month follow-up.

Results The iontophoresis patients had statistically significant improvement in grip strength at the conclusion of hand therapy compared with baseline. They were also more likely to get back to work without restriction. By 6-month follow-up, all groups had equivalent results for all measured outcomes.

Conclusions Dexamethasone via iontophoresis produced short-term benefits because for this group grip strength and unrestricted return to work were significantly better. This study suggests that this iontophoresis technique for delivery of corticosteroid may be considered a treatment option for patients with lateral epicondylitis. *(J Hand Surg 2012;37A:104–109.*

Type of study/level of evidence Therapeutic II.

Key words Corticosteroids, iontophoresis, lateral epicondylitis, randomized study.

Lateral epicondylitis is the most common overuse syndrome afflicting the elbow, with an incidence estimated at 4% annually.[1–3] This painful degenerative condition affects daily activities and work life. Although the condition is self-limiting in many, patients referred to surgeons often have had a prolonged disease course or multiple relapses. The spectrum of recommended treatment options includes patient education, behavioral modification, hand therapy, corticosteroid injection, and surgery.[4–7] Whereas literature can be found to support any number of interventions, there is a lack of prospective, randomized trials to guide treatment choices for lateral epicondylitis.[1,2] Despite the condition's prevalence and effect on work and lifestyle, little consensus exists on management. Surgery is usually reserved for recalcitrant cases. For most patients, the treatment aim is to break the cycle of pain using rest or medication and then slowly resume protected motion. Injection of corticosteroids is a standard intervention for pain relief for many enthesopathies including lateral epicondylitis.[4,7,8] Advocates can be found for all available corticosteroids. Recent studies suggest that lateral epicondylitis might not be an inflammatory process but a degenerative process, which would make the role of steroids more for pain relief

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than for an anti-inflammatory effect.[4] Although the use of steroids has short-term benefits, there are inherent risks to the use of an anti-vulnerary agent directly into the site of degenerative changes.[2,4] Steroid use can block the release of prohealing cytokines, thereby negatively impacting tissue's reparative ability.

Iontophoresis offers an opportunity to deliver medication without injection or deep penetration of the medication. It is a transdermal drug delivery method that uses a small electric current applied to the skin to drive the ionically charged steroid medication through the skin.[4,9] Evidence suggests that dexamethasone administration via iontophoresis is an effective, noninvasive means of decreasing acute pain in lateral epicondylitis.[1,10] Advantages of iontophoresis include its noninvasive nature, uniform absorption, and absence of systemic side effects such as gastrointestinal distress.[3,5] This study used an iontophoresis electrode and reservoir with an integrated battery that allows the treatment to be performed over 24 hours rather than the traditional 20 to 60 minutes. This device can potentially deliver higher levels of medication over 24 hours than in a traditional therapy session.

Because this innovation had not been studied for its utility in this patient population, we aimed to define the role of dexamethasone delivered via a self-contained iontophoresis device for patients with lateral epicondylitis. We hypothesized that dexamethasone via the iontophoresis battery patch would improve patient outcomes compared with local injection of corticosteroid medication.

MATERIALS AND METHODS

We performed a prospective randomized study in the outpatient setting between May 2006 and April 2009 at our urban institution. Three plastic surgeons participated in the study. The study was approved by the hospital's institutional review board and was listed on the National Institutes of Health clinical trial Web site (clinicaltrials.gov, number NCT00257634). We obtained informed consent from each subject.

Patients eligible for inclusion in the study ranged in age from 18 to 70 years, with a diagnosis of lateral epicondylitis made by local tenderness to palpation just distal and anterior to the lateral epicondyle. Provocative testing included pain with elbow extension, forearm pronation, and wrist flexion (Mille test), or pain with resisted extension of the middle finger (Maudsley test). Patients were excluded if they were pregnant, had a history of fibromyalgia or elbow surgery, had a duration of symptoms greater than 2 years, used steroid medication within the previous 6 months, or had bilateral involvement. We also excluded patients with bony abnormalities around the elbow or restricted elbow function.

The study design involved 3 treatment groups. Group 1 patients received the electronic transdermal drug delivery device (Iontopatch; Travanti Pharma Inc., Mendota Heights, MN) placed by the hand therapist. Using 10 mg dexamethasone placed in the reservoir, the iontophoresis patch remained in place for 2 days. A second patch was applied 2 to 10 days after removal of the first patch if the patient could not advance from the stretching phase to the strengthening phase of the therapy program because of pain. Group 2 patients received a 10-mg intramuscular/intratendinous dexamethasone injection (Bristol Meyers Squibb Pharmaceuticals, New York, NY) into the area of maximal pain. Group 3 patients received a 10-mg injection of intramuscular/intratendinous triamcinolone (Bristol Meyers Squibb Pharmaceuticals) into the area of maximal pain.

Patients were randomized during enrollment. We started hand therapy after randomization and standardized it for all 3 groups based on the published therapy protocol in Hunter and Callahan.[11] We divided the 8-week therapy protocol into 3 sections consisting of rest, mobility, and strengthening. Beginning in the rest phase, we treated randomized patients with 1 of the 3 medications described. During the mobility phase, patients were taught stretching exercises to increase range of motion. In the strengthening phase, patients were taught standardized exercises to increase strength and overall function. The strengthening phase began only after subjects were free of medication for 24 hours.

Primary outcome measures included grip strength change, and pain and function as measured by results of the patient-rated tennis elbow evaluation (PRTEE) questionnaire. The PRTEE is a validated patient outcome instrument specifically designed for lateral epicondylitis.[12,13] This was chosen for relevance to the disease process, high internal consistency, and highest responsiveness to change compared with many other validated questionnaires.[13] We tracked outcome measures at the beginning of the study (baseline), completion of treatment, and 6 months after treatment.

Patients ranked pain for a number of activities using a scale from 0 to 10, with 10 being the worst pain. Ten questions evaluated function in the affected limb. Higher scores on the function scale correspond to more difficulty completing activities of daily living.

Grip strength difference in elbow flexion and extension was performed in the manner outlined by Dorf et al.[14] We used change in grip strength because decreased strength with elbow extension can be diagnostic of

TABLE 1. Comparison of Treatment Groups

	Iontophoresis	Dexamethasone Injection	Triamcinolone Injection
Patients enrolled/completed (n)	35/31	32/27	34/28
Age (y)	41	42	46
Male (%)	58	52	48
Involvement of dominant hand	67	66	71
Work-related injury cases (n)	9	7	10
Duration before presentation (mo)	15	10	12
Employed (%)	82	85	87

lateral epicondylitis.[15] We measured grip strengths in the seated position with a hydraulic hand dynamometer (Jamar, Preston Rolyan, Bolingbrook, IL). Measurements were taken both with the elbow in 90° of flexion and with the elbow fully extended in front of the patient. We took care to ensure accurate limb positioning. At each encounter, patients performed 5 trials in each of the 4 positions: flexion and extension positions with the right arm and then with the left arm, for 20 attempts total.

Secondary outcome was work status. We regularly evaluated the patient's ability to work. We compiled these data into 3 categories: no work restrictions, work with restrictions, and no work.

Of the 101 patients recruited for the study, 86 completed therapy and 82 completed the study. Patients unable to complete therapy because of pain were considered treatment failures. Treatment failures included 3 patients in group 1 (dexamethasone via iontophoresis), 4 in group 2 (dexamethasone injection), and 2 in group 3 (triamcinolone injection). Two patients in the iontophoresis group received a second patch; both of these patients ended the study as treatment failures. Reasons for not completing therapy included patient noncompliance (6 patients) and treatment failure (9 patients). Four patients who completed the study were not reachable at 6-month follow-up and were excluded from analysis.

Statistical methods

We compared the serial differential grip strengths of the 3 treatment groups over the duration of the study using generalized estimating equations. This method takes into account multiple measurements on the same subject as well as the effects of treatment and time and the relationship between effect and time. This allowed estimations of whether the treatments followed similar trends over time.

We performed discrete data statistics using chi-square tests and performed continuous data analysis with analysis of variance. We determined sample sizes for chi-square testing based on a corticosteroid injection failure rate of 30% and a 20% difference in grip strength (flexion vs extension) in symptomatic lateral epicondylitis.[2,14] Power calculations were done for the recurrence of lateral epicondylitis. With this estimate and 25 subjects in each of the 3 groups, a recurrence rate of 30% or lower could be detected for the iontophoresis group, assuming an α of 0.05, power of 80%, and 2-sided testing. For the continuous measurement with 25 subjects per group, a mean difference between the 3 treatment groups of 0.63 or larger standard deviation units are detectable.

TABLE 2. Mean Percent Difference in Grip Strength From Flexion to Extension

	Baseline	Posttreatment	Study Conclusion
Iontophoresis	20 ± 4	12 ± 6[a]	1 ± 4[a]
Dexamethasone injection	18 ± 5	17 ± 5	12 ± 7[a]
Triamcinolone injection	19 ± 6	17 ± 7	8 ± 6[a]

Statistical significance is within the treatment group relative to baseline value.
[a]$P \leq .001$.

RESULTS

Chi-square analysis showed the 3 groups were similar with respect to age, gender, involvement of dominant hand, duration of symptoms, and percentage of subjects employed (Table 1). We measured differential grip strength (flexion vs extension) at the 3 time points. The iontophoresis group had statistically significant improvement for this measured outcome both at the end of treatment and at the end of the study. The other 2

TABLE 3. Pain Rating Using the PRTEE Questionnaire

Treatment Group	Baseline	Posttreatment	Study Conclusion
Iontophoresis	7.2 ± 2.7	5.7 ± 3.1[a]	5.7 ± 1.8[a]
Dexamethasone injection	7.6 ± 2.9	6.7 ± 2.6[a]	6.5 ± 1.6[a]
Triamcinolone injection	6.9 ± 2.1	6.3 ± 3.3[a]	5.6 ± 2.5[a]

All groups reached statistical significance based on mean changes relative to baseline values.
[a]$P < .05$.

TABLE 4. Function Rating Using PRTEE Questionnaire

Treatment Group	Baseline	Posttreatment	Study Conclusion
Iontophoresis	5.3 ± 3.4	3.5 ± 2.5[a,b]	3.6 ± 2.1[a]
Dexamethasone injection	5.4 ± 3.7	4.9 ± 2.6[a]	4.5 ± 1.7[a]
Triamcinolone injection	5.0 ± 3.6	4.7 ± 2.1	4.2 ± 2.0[a]

Statistical significance based on mean changes relative to baseline values.
[a]$P < .05$.
[b]Pearson correlation = 0.77.

groups attained significant improvement by the end of the study but not at the end of therapy (Table 2). Because a substantial difference between grip strength with elbow flexion and extension can be diagnostic of lateral epicondylitis, a small difference between the 2 positions implies less pain.

The PRTEE questionnaire has 2 subcategories: pain and function. All 3 groups had statistically significant improvement in pain at the end of therapy and at the conclusion of the study (Table 3). The mean change in pain scale (of all the groups) from baseline to conclusion was 1.3. We noted statistically significant improvement in function for groups 1 and 2 after treatment and all 3 groups at the 6-month follow-up (Table 4). Mean change in function scale (of all the groups) from baseline to conclusion was 0.9. We calculated the correlation coefficient for each time point and subscales. We noted a significant positive correlation (>0.50) for the iontophoresis group in the function subscale at the 6-month follow-up.

Each patient and physician (not blinded to treatment) determined change in work status jointly. Improvement in work status was statistically significant for the iontophoresis group at both treatment end and 6-month follow-up (Table 5). In all cases, the patients and employers accepted the work restrictions and work status.

Across all groups, 7 patients required surgical intervention owing to persistent symptoms. These patients underwent extensor carpi radialis brevis tendon release. Within each treatment group, there were too few patients who required surgery to perform appropriate statistical analysis. By combining the surgery patients into a single group, we could compare them to a random sample of patients not treated with surgery from any of the 3 groups. Therefore, we performed Student's *t*-test to compare equality of means with a randomly chosen sample of 7 patients who did not undergo surgery. We compared demographic, medical, and perioperative findings of the 2 cohorts to identify differences. One statistically significant finding was identified. Patients whose grip strength improved less than 15% after therapy relative to baseline were more likely to undergo surgical intervention ($P < .035$).

Complications were few. Less than 10% of patients treated with injection reported postinjection pain, which completely resolved for all within 2 days. One iontophoresis patient developed skin irritation from the second iontophoresis patch, which resolved 3 days after the patch was removed. Because this patient had a history of dexamethasone injection, we believe the iontophoresis patch most likely caused the reaction. Two patients had minor irritation from shaving of the arm for patch application. This did not interfere with placement or use of the iontophoresis patch.

DISCUSSION

Self-contained iontophoresis is an intriguing development for the delivery of transcutaneous medication. It represents a less invasive and potentially more efficacious treatment option. Corticosteroid injection remains a frontline intervention for lateral epicondylitis even though recent reports have suggested that this treatment produces no sustained benefit.[16,17] An alternative delivery method for this class of medication is the integrated battery iontophoresis system. This system allows medication delivery in a sustained and painless manner and frees the therapist to spend more time on therapy compared with using 20 minutes or more to administer the medication via traditional iontophoresis.

One reason why steroid injections may not be efficacious in the long term is that injection of corticosteroids into the site of deep tissue damage may be detrimental. If lateral epicondylitis is a degenerative rather

TABLE 5. Work Status Change

Treatment Group	Work Status	Baseline	Posttreatment	Study Conclusion
Iontophoresis	No restriction	40%	52%[a]	82%[a]
	With restriction	54%	42%	18%
	No work	6%	6%	0%
Dexamethasone injection	No restriction	42%	33%	64%
	With restriction	51%	52%	29%
	No work	7%	15%	7%
Triamcinolone injection	No restriction	40%	36%	60%
	With restriction	56%	50%	33%
	No work	4%	14%	7%

Baseline value determined after initial consultation.
[a]$P < .05$. Significance is relative to baseline work status without restriction within the treatment group.

than inflammatory process, the medication may delay healing.[18] Although steroid injections can provide short-term relief,[19–21] once the analgesic effect of the medication subsides, the pathology remains unchanged. Therefore, injection puts a high concentration of corticosteroids at the site of degeneration and may interfere with long-term healing.

If lateral epicondylitis is not an inflammatory process, why do corticosteroids work at all? Alfredson and Lorentzon[18] have shown that glutamate is often abundant at sites of enthesopathies (including lateral epicondylitis) even though there are no inflammatory cells or cytokines. The presence of the neurotransmitter glutamate is responsible for pain signaling in these enthesopathies. Glutamate and its receptors can be blocked by corticosteroids and reduce pain at the site.

The lack of long-term benefit from corticosteroid therapy may have more to do with the delivery method than the medication. We use corticosteroids in lateral epicondylitis with the goal of breaking the cycle of pain long enough for patients to participate in therapy and effectively adopt corrective behavior modifications. Long-term recovery may come from protection of the extensor carpi radialis brevis followed by re-education and healing.

Reports suggest that most patients with lateral epicondylitis will improve regardless of which corticosteroid or treatment modality is used.[2,7,17,21] In our study, patients treated with iontophoresis improved faster than the other groups. Pain rating statistically improved for all groups, although changes over time and between groups may not have been clinically significant. The iontophoresis group had significant improvement in grip strength at 6 weeks relative to the other groups. For the PRTEE results, the iontophoresis group did as well as or slightly better than the injection groups at both time points. Iontophoresis patients were also more likely to return to work without restrictions, compared with patients receiving injection with either dexamethasone or triamcinolone. Although many patients converted from no work to work with restriction, we avoided commenting on this owing to a lack of validated methodology for assessing stepwise improvement in work status.

One limitation of iontophoresis is the type of medications used. Properties include water solubility, molecular size, and ionic charge.[9] Many physicians prefer a longer-acting glucocorticosteroid (such as triamcinolone) for the treatment of enthesopathies. For these reasons, dexamethasone is the only practical choice for iontophoresis. To better compare the mode of delivery, we added the third arm of dexamethasone injection in the study design. Our results suggest that the 2 injection groups had similar outcomes. This confirms that the method of medication delivery may be more important than the specific medication used. In a clinical setting, additional corticosteroid injections are offered for incomplete relief. We did not offer this option. Additional injections may have skewed the results in favor of the injection groups. There are certainly nuances of iontophoresis that may vary between the 24-hour patch and the traditional system. Nevertheless, we believe that the principle at work is the delivery system for corticosteroids. More questions may have been answered by using a no-treatment group and also by using a placebo-based iontophoresis control group because uncertainty

remains regarding whether the effects seen were related to drug delivery, electrical stimulation, time, activity modification, or therapy. Ethically, we did not believe that a no-treatment arm was a realistic option. Although the study was randomized, the participants were not blinded with respect to the treatment arms. An additional limitation is that our follow-up rate after 6 months dropped off considerably, making analysis beyond this time point impractical. We therefore limited our inquiry to the short-term findings. We have also considered whether the iontophoresis group improvements were achievable independent of the therapy. A patient-managed iontophoresis protocol without formal therapy may produce similar results.

Another limitation of the study was that the population that underwent surgery within each group was too small for comprehensive comparison. We therefore relied on a random sample of all nonoperative patients to serve as a comparison for the extensor carpi radialis brevis tendon release cohort. This comparison revealed that the surgically treated patients were significantly weaker both after treatment and at the end of the study than the no-surgery patients. In our population, the weaker patients required surgery. This is not surprising. Because they did not reach an acceptable level of function with corticosteroid and therapy, surgery was a reasonable option.

The iontophoresis patch with an integrated battery offers technical and lifestyle advantages over traditional iontophoresis. In the traditional form, the external battery requires the therapist to turn up the current slowly and requires 20 to 30 minutes to deliver the medication. With this iontophoresis patch, the patient has the medication and patch applied at the start of the appointment. Valuable therapy time can be used for education, instruction, and therapy.

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