Use of Hyaluronic Acid Gel Filler versus Sterile Water in the Treatment of Intractable Plantar Keratomas

A Pilot Study

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Background: Intractable plantar keratoma is a common concern in the podiatric medical office. Different treatment options are available, ranging from trimming and padding to surgery. We sought to investigate the use of hyaluronic acid gel injections as a possible minimally invasive alternative in the treatment of intractable plantar keratomas.

Methods: Seventeen patients with intractable plantar keratomas were randomly assigned to receive a hyaluronic acid gel injection or a sterile water injection at the site of a previously trimmed plantar lesion.

Results: There was no significant difference between the two groups in the evaluation of pain and function at 12 weeks, but both groups showed a clinically relevant improvement. No significant change was observed in plantar tissue thickness in both groups. A minor adverse reaction was seen in the hyaluronic acid group.

Conclusions: The use of a hyaluronic acid gel injection at the site of a trimmed intractable plantar keratoma did not seem more effective than the use of a sterile water injection. Sterile water injections seemed safe and efficient in reducing pain associated with plantar keratomas. Further investigations should concentrate on whether these results are reproducible in a larger sample and on the most effective sequence of treatment. (J Am Podiatr Med Assoc 105(1): 22-26, 2015)
collagen production at the injection site. Naturally occurring in soft tissues, hyaluronic acid gel contributes to resilience of skin as it possesses a unique dynamic viscosity and locally attracts water molecules.\textsuperscript{17,19}

We, therefore, investigated the safety and efficacy of hyaluronic acid gel injections at the plantar surface to reduce the symptoms associated with long-standing IPKs. We hypothesized that hyaluronic acid gel injections would reduce the pain and help restore skin integrity at the site of IPKs.

**Methods**

This was a prospective, one-center, randomized, controlled, double-blind pilot study. All of the participants gave their written informed consent to participate in this study, which was approved by the Université du Québec à Trois-Rivières Ethics Committee (Trois-Rivieres, Quebec, Canada). Adults presenting with one or more painful IPKs for at least 3 months were considered for the study. The IPKs were defined as nucleated calluses plantar to the condyles of an overlying metatarsal head. Patients were required not to have any concomitant foot infection or ulceration or any other serious medical conditions. Participant characteristics by study group are presented in Table 1.

After written informed consent was obtained, patients were randomly placed in either the hyaluronic acid group or the sterile water group. The assignments, which were generated by a computer, were presented in sealed, sequentially numbered envelopes. Nine and eight patients were placed in the hyaluronic acid and sterile water groups, respectively. All of the participants were interviewed and evaluated at the university podiatric medical clinic before the intervention. Demographic information was collected to compare this sample with the general population of patients with IPKs. A podiatric physician (M.B.-F.) conducted brief dermatologic, biomechanical, vascular, and neurologic examinations, including the Semmes-Weinstein monofilament test. Documentation of adequate macrovascular arterial perfusion was made to prevent application of the projected technique in contraindicated circumstances. Foot radiographs were taken to rule out any structural deformity that could have contributed to the pathologic abnormality. All IPKs on the patients’ feet were debrided using a scalpel, and then enucleation was performed with a water-spraying drill.

At the first visit, each patient identified the lesion recognized as the most painful. After debridement, initial weightbearing plantar soft-tissue thickness underneath this lesion was measured using a LOGIQ e ultrasound (GE Healthcare Technologies, Waukesha, Wisconsin) and a validated technique.\textsuperscript{20} Then, local skin anesthesia was obtained using 1.0 to 3.0 mL of lidocaine, 1% plain, and bupivicaine, 0.5%, with epinephrine, 1:200,000, in a 2:1 ratio injected proximal to the trimmed IPK. The experimental intervention consisted of one injection of 0.5 to 1.0 mL of hyaluronic acid gel (ReDexis Ultra; Prolle-nium Medical Technologies Inc, Toronto, Ontario, Canada) or sterile water at the subcutaneous-dermal junction underneath the center of the

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the Study Groups</th>
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<tr>
<td>Characteristic</td>
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<tr>
<td>Female sex (No.)</td>
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<tr>
<td>Injection site (No.)</td>
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<tr>
<td>First metatarsal head</td>
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<td>Second metatarsal head</td>
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<td>Third metatarsal head</td>
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<td>Fourth metatarsal head</td>
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<td>Fifth metatarsal head</td>
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<td>Age (years)</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>Body mass index (kg/m(^2))</td>
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<tr>
<td>Smokers (No.)</td>
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<td>Time since beginning of symptoms (years)</td>
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<td>Cutaneous plantar sensibility with Semmes-Weinstein monofilament at time 0 all sites added (g)</td>
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Note: Data are given as mean (range) except where indicated otherwise.
trimmed lesion. The syringe plunger was pressed until the plantar skin began to blanch and the tissue deficit was almost entirely filled. Another plantar tissue thickness measure was taken immediately after injection of the dermal filler. At that same visit, patients were also asked to rate their initial pain level on a visual analog scale (VAS) and to complete a written questionnaire, translated into French and shortened to 27 questions, adapted from a validated foot pain questionnaire, the Revised Foot Function Index (FFI-R). This questionnaire was divided into three separate subscales (pain, disability, and activity restriction) that were analyzed individually. On each subsequent visit, at 1, 4, 8, and 12 weeks after injection, patients had to complete the VAS and the FFI-R, and a plantar tissue thickness measure was again taken.

Patient characteristics of the two groups were compared using the Student t test. Two-way (group × time) repeated-measures analyses of variance were conducted for each dependent variable (VAS score, FFI-R, and plantar tissue thickness). When necessary, Fisher least significant difference post hoc analyses were made. Missing data were managed by replacing the data by the group mean. The significance threshold was established at 5% for all of the analyses.

Results

No safety concerns were reported in either the hyaluronic acid or the sterile water group; only one minor adverse reaction was recorded. A small hematoma formed at the site of injection in one patient in the hyaluronic acid group. This patient presented many risk factors for complications, including a high body mass index, active tobacco use, and postinjection prolonged standing. The hematoma was easily drained, and follow-up took place as planned.

No differences were observed in pain reduction between the two groups on the VAS (P = .459); in the entire study population, there was a trend toward pain reduction, which peaked at the 4-week visit and then slowly increased but never reached baseline levels. Observed VAS scores at weeks 1, 4, 8, and 12 were significantly reduced from baseline for both groups (P < .01) (Fig. 1).

The analysis revealed a significant difference between groups for the FFI-R pain subscale (P < .05) (Fig. 2) and disability subscale (P < .01) (Fig. 3) but not for the FFI-R activity restriction subscale (P = .250) (Fig. 4). A main effect of time was also observed for all of the FFI-R subscales (P < .01).

Figure 1. Box plot of change in mean visual analog scale (VAS) scores in the sterile water and hyaluronic acid groups between each visit. The top border of the box marks the 75th percentile. The whisker above the box marks the 90th percentile.

Figure 2. Box plot of change in mean Revised Foot Function Index (FFI-R) pain subscale scores in the sterile water and hyaluronic acid groups between each visit. The top border of the box marks the 75th percentile. The whisker above the box marks the 90th percentile.
significant ($P > .05$) group and time effect was observed for plantar tissue thickness (Fig. 5).

The relationship between the baseline pain score on the VAS and plantar tissue thickness was also nonsignificant ($P = .940$). Finally, no significant ($P > .05$) interaction effect between the factors group and time was observed for VAS scores, all of the FFI-R subscales, and plantar tissue thickness.

**Discussion**

Although plantar hyaluronic acid gel injection seems safe, it also seems to be as effective as sublesional sterile water injection in the treatment of IPKs. Indeed, the comparison group in this study unexpectedly produced a similar decrease in reported symptoms. The mean pain reduction reported by these patients was more than four times what is considered clinically relevant on the VAS.22 These results also qualify as clinically significant according to a recent publication dedicated to the interpretation of FFI-R scores.22 Larger and longer clinical trials are needed to confirm the results of this pilot study. Future research concerning sterile water injections may be indicated by an investigation of saline water injection for the treatment of cutaneous atrophy after corticosteroid injection.23 The authors of this small study obtained significant results at restoring facial lost volume with repeated injections of intraleisional sterile water.

Although plantar tissue thickness data sampling encountered technical difficulties that requires careful interpretation, the discovery that hyaluronic acid gel injection did not result in a thicker plantar fat pad seems logical considering its dynamic viscosity property.17 We believe that the shear force
that is applied to the foot plantar surface when walking is responsible for the immediate liquefaction and, therefore, dispersion of the hyaluronic acid gel at the injection site. This could explain why no difference in plantar tissue thickness was observed between the two groups even a few minutes after the injection. Hyaluronic acid gel does not act much differently than water when injected at the plantar surface. However, this product could still represent a possible treatment material for dermatologic lesions where there is a loss of substance located on a nonweightbearing area of the foot, such as the dorsal foot or toes or interdigitally.

Although plantar tissue thickness is not increased, by using plantar sterile water injections as a treatment alternative for IPKs it may be increased, by using plantar sterile water injections.

Financial Disclosure: The hyaluronic acid gel used for this trial was provided by Prolenium Medical Technologies Inc, the manufacturer of ReDexis Ultra. The sponsor had no role in the collection, analysis, and interpretation of the data or in the preparation of the manuscript.

Conflict of Interest: None reported.

References


