ABSTRACT

Background
The effectiveness of corticosteroid injection for the treatment of Morton’s neuroma is unclear. In addition, most of the studies related to it are case-control or retrospective case series.

Methods
Forty-one patients with a diagnosis of Morton’s neuroma were randomized to receive three injections of either a corticosteroid plus a local anesthetic or a local anesthetic alone. The Patients and the researcher who collected data were blinded to the treatment groups. The Visual Analogue Scale (VAS) for pain and the American Orthopedic Foot and Ankle Score (AOFAS) were obtained at baseline, after each injection and at 3 and 6 months after the last injection.

Results
There were no significant between-group differences in terms of pain and function improvement at three and six months after treatment completion in comparison to baseline values. At the end of the study, there were 17 (48.5%) patients requesting surgical excision of the neuroma: seven (44%) in the experimental and ten (53%) in the control group ($p=1.0$).

Conclusions
The injection of a corticosteroid plus a local anesthetic is not superior to a local anesthetic alone in terms of pain and function improvement in patients with Morton’s neuroma.

Level of evidence
Level I, randomized controlled trial

Keywords
Morton’s neuroma; Injection; Corticosteroid; Local anesthetic.
INTRODUCTION

Morton’s neuroma is a common cause of forefoot pain and is frequently resistant to the different proposed treatments. The diagnosis of Morton’s neuroma is essentially clinical, but both ultrasound and magnetic resonance imaging (MRI) are often used to confirm the diagnosis in atypical cases. In addition, imaging studies are useful to determine the exact location of neuromas, quantify their size and to rule out associated conditions.

The initial treatment of choice is nonoperative. In case of failure of conservative treatment with orthotics and adequate footwear modifications, the most common treatment used historically has been operative excision of the neuroma. The results of operative treatment are varied and rarely exceed 80% in terms of satisfaction.

Corticosteroid injections have been used as a preliminary step to surgical treatment after failure of orthotics or footwear modifications and even as a first-line therapy. Even so, the studies published to date show few predictable results and there is no clear evidence as to the effectiveness of such infiltrations. Patient satisfaction after infiltration is highly variable and while all patients do not improve, this technique can be considered for the temporary relief of symptoms. In 2004, a systematic review concluded that there was not enough evidence to recommend corticosteroid injections for the treatment of Morton’s neuroma due to a lack of well-designed randomized studies. Subsequently, the same group published a randomized controlled trial involving 131 patients to determine the effectiveness of corticosteroid infiltration in Morton's neuroma. In that trial, there were no superior results of corticosteroid infiltrations over the control group at one year. The study was only patient-blinded and further reproducibility studies have not been conducted.

The principal purpose of this study was to compare the effectiveness of a corticosteroid injection associated with a local anesthetic against a local anesthetic alone (placebo control group) for the treatment of Morton's neuroma. Our hypothesis was that patients infiltrated with corticosteroids experience a significant improvement in pain relief at three and six-month follow-up when com-
pared to the placebo control group. The secondary purpose was to evaluate the influence of age, sex, body mass index (BMI), injured side, duration of symptoms, size and location on the outcomes of Morton’s neuroma after the treatments.

MATERIAL AND METHODS

Procedures

A prospective double-blinded randomized placebo controlled trial was designed to respond to the research question. Between January 2013 and January 2015, all patients seen in the outpatient clinic with a diagnosis of Morton’s neuroma were potentially included. The diagnosis of Morton’s neuroma was characterized by plantar pain and tenderness affecting the web space, along with one of the following clinical findings: 1) paresthesia in the second and/or third interdigital space of the foot; 2) worsening of symptoms upon weight-bearing or with certain/tight footwear; 3) clinical improvement after removal of conflicting footwear or after massage; and 4) positive metatarsal compression test (painful) or 5) a palpable and/or painful click (positive Mulder's sign).^{21,24}

Patients with a clinical diagnosis of Morton’s neuroma were included if they were 18 years old or more, had failed to improve with adequate conservative treatment and had met none of the exclusion criteria. The criteria were 1) patients who had received previous injections for this condition or who were under other current treatment for the neuroma, 2) the presence of two lesions on the same foot as well as the presence of systemic diseases such as rheumatoid arthritis or associated injuries in the metatarsophalangeal joints (synovitis, stress fracture, osteonecrosis, etc.), 3) the presence of any condition that might lead to complications in the infiltration such as infection in nearby tissues, patients taking anticoagulants or an allergy or hypersensitivity to any component 4) and patients under concomitant treatment with analgesics, anti-inflammatory or neuromodulators for other conditions.
All patients eligible for inclusion were invited to participate in the study and provided with a study description including the specification about the randomization process and blinding to receive one of the two treatments. After the patients had read the study protocol, questions and discussion with study members were allowed and written informed consent obtained. Once patients were included in the study and clinically diagnosed, an MRI without contrast was obtained to confirm the presence of the neuroma, localize it and rule out other conditions. Additionally, the size was quantified in centimeters by a musculoskeletal radiologist. All patients were offered surgical excision at the completion of the study if they were still symptomatic or dissatisfied with the results. The present study received the approval of our Institutional Review Board before commencement.

All patients included in this study were randomized to the treatment or control group. A computer-based randomization process was employed by using a specific computer program that was only accessible to the Pharmacy Department providing the medications. The researcher who performed the infiltration was different from the one who collected the data. Both the patients and the researcher who collected the data were blinded to treatment assigned. The pharmacy provided the syringes that came in an opaque vial so as to mask it to the physician performing the infiltration. A triple-blinded study had been initially planned. However, blinding of the physician performing the injection did not turn out to be possible because of the visible differences in the color and density of the residual liquid of the two compounds seen on the skin at the end of the infiltration.

All patients included in this study had five clinical visits scheduled. At the first clinical visit (V1), pre-infiltration study variables were collected and the 1st infiltration was carried out. The second visit (V2) was scheduled a week later to receive the 2nd infiltration. The third visit (V3) occurred two weeks after the first one, when patients received the last injection. After treatment completion, patients were scheduled for a follow-up appointment at 3 months (the fourth visit, V4) and 6 months (the fifth visit, V5) after the first injection. Study variables were collected at all clinical visits.
Participants

Seventy-four patients with a clinical diagnosis of Morton's neuroma were identified over a period of two years (2013-2015) in our department. Ten patients chose not to participate in the study after being presented with the proposal. Of the remaining 64 patients, 23 presented one or more of the exclusion criteria and were not included. The final sample was left with 41 randomized patients (20 in the experimental group and 21 in the control group). Four patients from the experimental group and two patients from the control group withdrew from the study or were lost in the follow-up. The final sample included 35 patients: 16 in the experimental group and 19 in the control group (Figure 1). Demographic and injury characteristics from both groups are compared in Table 1.

Treatment methods

The experimental group consisted of three injections of 2ml of a corticosteroid plus an anesthetic (1 ml Mepivacaine 2% + 1ml Triamcinolone 40mg) for each one. The control group consisted of three injections of 2ml of 2% Mepivacaine for each patient. The three injections were given one week apart. Rescue pain medication was provided to patients (Ibuprofen 600 mg, every 8 hours), as needed. Patients were instructed to register all the pain medication taken during the study period.

All the injections were performed in the outpatient clinic by two foot and ankle specialists following the same protocol. Aseptic conditions were assured with use of iodine and sterile latex/nitrile gloves. Then, the infiltration was performed via dorsal "locus dolentii" in the intermetatarsal space without the aid of ultrasound.

Study variables

The primary outcome of the study was the Visual analog scale (VAS) for pain. The patient stated what their pain was like on a scale from 0 to 100 (mm) where 0 was "no pain" and 100 was "the worst imaginable pain." A major functional outcome was the American Orthopedic Foot and
Ankle Score (AOFAS) Clinical Rating System test (metaphalangeal and interphalangeal score).\(^{16}\)

This scoring system consists of numerical values ranging from 0 to 100 where 100 means no functional limitations, pain or deformities. Patients' satisfaction was evaluated with the Modified Johnson scale: 1) Completely satisfied; 2) satisfied with minor reservations; 3) satisfied with great reservations; 4) dissatisfied; and 5) I wish I had never had the infiltration.

The secondary variables collected included: 1) baseline demographic characteristics (age, gender, BMI) of the sample; 2) duration of symptoms; 3) size (in cm) and location of the neuroma according to the MRI; 4) the presence of radiating pain, paresthesia or a positive Mulder's sign; and 5) the need for pain medication after injection.

**Statistical analysis**

The power analysis performed determined that a sample of 32 patients (16 per group) was needed to obtain differences of 30mm on the VAS scale for pain with a statistical power of 80% and a significance level of 5%. Considering an estimated 20% loss of patients at follow-up, a minimum sample size of 40 patients (20 per group) was determined. The participants were analyzed in the groups to which they had been assigned (randomized) following the intention to treat principle.

To analyze the between-group differences in pain (VAS) and function (AOFAS) and the influence of secondary variables on them, the Mann-Whitney test was used. For the analysis of between-group differences of dichotomous variables, the chi-square test was used. A Spearman’s correlation coefficient was used to analyze the relationship between quantitative variables. The statistical analysis was conducted using the SPSS v.21 package (SPSS Inc., Chicago, IL, USA). The alpha level was set at .05.

**Financial information**

This study received no funding and was of no cost to patients.
RESULTS

Both groups were compared for demographic data and injury characteristics at the beginning of the study, being both groups comparable for those variables (Table 1).

The comparison of VAS for pain and AOFAS between the two groups for each study period is shown in Table 2. The most significant VAS and AOFAS improvement for both groups was observed at 3 months after treatment completion (Table 3). There were no between-group differences found relative to the need for rescue analgesia ($p=0.685$). Table 4 summarizes the influence of demographic and injury characteristics on the differences in VAS and AOFAS between the baseline (V1) and the last follow-up at six months (V5). A significantly better response to the treatment relative to pain and AOFAS was seen in older patients ($p=0.018$ for pain and $p=0.002$ for AOFAS) and patients with a shorter duration of symptoms ($p=0.047$ for pain and $p=0.048$ for AOFAS). In addition, patients with an absence of radiating pain at the beginning of the study had better improvement in pain after six months ($p=0.027$).

There were no statistically significant differences in the degree of satisfaction at six months between both groups ($p=0.744$). In the steroid group, six patients (37.5%) were satisfied, four (25%) were satisfied with minor reservations, three (19%) were satisfied with great reservations and two (12.5%) were dissatisfied. One patient (6%) said "I wish I had never undergone the infiltration". In the control group, six patients (32%) were satisfied, five (26%) were satisfied with minor reservations, three (16%) were satisfied with great reservations and five (26%) were dissatisfied. No patients said "I wish I had never undergone the infiltration." Considering 0 to 2 points in VAS a complete or near complete response to the treatment, nine patients in the steroid group (56%) and seven patients in the control group (37%) reached that improvement at six months. At the end of the study, there were 17 (48.5%) patients requesting surgical excision of the neuroma: seven (44%) in the steroid group and ten (53%) in the control group ($p=1.0$). Three (18.7%) of the patients in the steroid group had mild skin atrophy at the area of infiltration that did not require any action and it
did not affect deeper levels or the fat pad. No other adverse effects or complications were seen during the study.

**DISCUSSION**

The principal finding of this study was that a corticosteroid plus a local anesthetic injection did not show any advantage compared to a local anesthetic alone in the treatment of Morton’s neuroma. These results are largely consistent with those published in the literature to date.\(^\text{10, 22, 23, 25, 26}\)

Several studies have observed that the benefits of corticosteroid injections are only immediate or short-term.\(^\text{10, 22, 23, 25, 26}\) The present study demonstrated that the steroid group maintained a significant intra-group improvement in the VAS over the six months in comparison to the control group where the intra-group improvement in terms of pain was only significant at three months. The difference between the initial and final follow-up was only statistically significant in the steroid group (p=0.012). Nevertheless, the significant inter-group differences were only in the first week. This means that the corticosteroid injections have a beneficial immediate effect over the placebo. However, this beneficial effect on pain is diminished after a short period of time. Although the greatest improvement occurred between baseline and three months, improvement in the VAS for pain at six months was still clinically relevant, as the reduction is superior to 33% from baseline.\(^\text{15, 28}\)

In contrast, AOFAS showed an isolated significant intra-group improvement at three months in both groups (with a modest intra-group improvement maintained over time in both groups) with no inter-group statistical differences. Despite the relevant intra-group improvements, it does not appear to influence final patient outcomes and surgical rates between groups.

Thompson et al. observed significantly better patient global assessment of foot health and some of the parameters of the Manchester Foot Pain and Disability Schedule (MFPDS) and the Multidimensional Affect and Pain Survey (MAPS) at one and three months after corticosteroid and anesthetic injection compared to an anesthetic alone. Nevertheless, significant differences were not
maintained at one year after treatment.\textsuperscript{25} Thus, these results were similar to those obtained in the present study, which were an improvement in pain and AOFAS for both groups at the short follow-up (up to three months) with no differences between them at six months. The greatest improvement in pain and AOFAS was seen at three months, but then a slight non-clinically relevant decrease in both values was observed at six months. This is consistent with previous findings of positive results with infiltrations in the short term, worsening later with virtually no effect at one year of infiltration.\textsuperscript{22}

The significant and long-lasting improvement in pain and the AOFAS as well as satisfaction demonstrates a possible placebo effect in the control group. As described in the literature, the placebo effect may be superior in studies performing multiple repetitions of a treatment.\textsuperscript{11,19} This seems particularly true for satisfaction as patients receiving multiple infiltrations seem to show higher satisfaction values compared to those receiving only one injection.\textsuperscript{2,5,9,10,12,22,23} This is one of the causes for using multiple injections in some trials, including the present study. Therefore, this hypothetical placebo effect was created in both groups so that a bias could be prevented.

The significant negative correlation between age and the differential VAS for pain (V5-V1) suggests that corticosteroid injections may not be as beneficial for younger people compared to older individuals in terms of pain relief. Moreover, the same may be applied for the AOFAS as older individuals had higher AOFAS differentials (V5-V1). To our knowledge, this is the first study to have observed a difference in the response to injections for Morton’s neuroma related to age. With regard to the duration of symptoms, a significant positive correlation with differential (V5-V1) pain levels associated with a significant a negative correlation with the differential (V5-V1) AOFAS may indicate that patients with long-term pain might be worse candidates for corticosteroid injection to obtain pain relief and a better AOFAS. This finding is similar to that found by Bennett et al. They found that patients with symptoms of less than one year’s duration appeared to do better than those with symptoms of more than one year’s duration.\textsuperscript{2} Both findings seem to suggest that older
patients with a shorter duration of symptoms may be candidates for corticosteroid injections for the
treatment of Morton’s neuroma

To the best of our knowledge, this is the first study to investigate, through a randomized
controlled trial, the influence of sex, BMI, size and location of the neuroma on the outcomes of corti-
costeroid injection. The present study could not find a significant influence of these parameters on
the treatment of Morton’s neuroma through injections. Other authors have observed an influence of
the size of the neuroma on the outcomes of surgical treatment. Sharp et al. reported that excision of
larger lesions led to higher cure rates than the removal of smaller lesions.24 On the other hand, Bias-
ca et al reported that lesions of less than 5mm in size that produced metatarsalgia were treated suc-
cessfully with neurolysis and division of the intermetatarsal ligament whereas larger lesions were
treated with excision.3 A reasonable management strategy would be to perform injections in smaller
lesions and to plan on excision for larger ones. However, this strategy still needs to be proven in
adequate high-quality studies.

Some studies have recommended that the injections should be performed by radiologist un-
der ultrasound guidance through the plantar aspect of the foot.10,12,25 In our opinion, this technique
might make it easier to target the “hot spot” that causes patients’ symptoms rather than blind injec-
tions. However, this technique is operator-dependent and does not show the reality in most clinical
practices where a radiologist may not be easily or readily available in the outpatient clinic. This
makes for the current practice of performing a dorsal blind injection without the assistance of ultra-
sound in many departments. Therefore, the fact that 9 patients in the steroid group (56%) and 7 in
the control group (37%) had an excellent response to the treatment at 6 months (considering a final
VAS between 0 and 2 points) supports the effectiveness of a blind injection.

The present study has some limitations. First, the follow-up was only 6 months. Despite it
being considered short and that outcomes may worsen with a longer follow-up; 6 months would be
enough to evaluate whether corticosteroid injection is effective for the treatment of Morton’s neu-
roma. A prolongation of the study was discussed, but it was finally decided not to prolong the fol-
low-up given the results obtained at six months which demonstrated stabilization of the improve-
ments as previously found by other authors with a one year follow-up period. Second, the physi-
cians performing the injections were not blinded to the treatment group, which could unintentional-
ly influence the outcomes. However, care was taken not to break patient-blinding and not affect
their perception or create any type of influence on the outcomes. Third, performing multiple injec-
tions increased the risk of losing patient-blinding, but we are unaware of any patient finding out to
which group had been they allocated before the completion of the study. Fourth, no objective out-
comes were obtained after the treatment (i.e., MRI evaluation). However, the most important aspect
in the treatment of Morton’s neuroma is the subjective improvement of symptoms in patients. Fifth,
the reliability and responsiveness of AOFAS test has not been confirmed, but the subjective com-
ponent (pain) of this score was evaluated by Ibrahim et al. Moreover, it has been widely used in
the published literature related to the foot and ankle, at least up to the moment that we conducted
the study.

On the other hand, this study is a prospective randomized double-blinded placebo-controlled
trial involving a sample size big enough to detect significant differences. Therefore, the methodolo-
gy of the study makes conclusions potentially more robust compared to previous studies.

Conclusion

The injection of a corticosteroid plus a local anesthetic is not superior to a local anesthetic
alone in terms of pain and function improvement in patients with Morton’s neuroma. The benefits
of corticosteroid injections are short term and patients should be advised that they may likely need
surgical excision. Older patients without a prolonged period of pain may more likely benefit from
injections when compared to their younger counterparts.

REFERENCES


Figure and table legends

Figure 1. Flow diagram with the enrollment, randomization, follow-up and analyzed patients.

Table 1. Comparison of demographic and injury characteristics between the experimental and control groups.

Table 2. Comparison of the Visual analogue (VAS) scale for pain and American Orthopedic Foot and Ankle Score (AOFAS) between both groups for each study period.

Table 3. Comparison of intra- and inter-group differences on the visual analogue scale (VAS) for pain and American Orthopedic Foot and Ankle Score (AOFAS) between baseline (V1) and the rest of the study periods.

Table 4. The influence of demographic and injury characteristics on the Visual analogue scale (VAS) for pain and American Orthopedic Foot and Ankle Score (AOFAS) differences between the baseline (V1) and six months (V5).