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Corticosteroid Injection for the Treatment of Morton's Neuroma: A Prospective, Double-Blinded, Randomized, Placebo-Controlled Trial

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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. The purpose of this study was to compare the effectiveness between corticosteroid injection associated with local anesthetic and local anesthetic alone (placebo control group) for the treatment of Morton's neuroma.

Methods: Forty-one patients with a diagnosis of Morton's neuroma were randomized to receive 3 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 analog scale for pain and the American Orthopaedic Foot & Ankle Score (metatarsophalangeal/interphalangeal score) 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 3 and 6 months after treatment completion in comparison with baseline values. At the end of the study, 17 (48.5%) patients requested surgical excision of the neuroma: 7 (44%) in the experimental group and 10 (53%) in the control group ($P = 1.0$).

Conclusion: The injection of a corticosteroid plus a local anesthetic was 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.[8,14,18,30] 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 rule out associated conditions.[4,17,24,29,31]

The initial treatment of choice is nonoperative. In case of failure of nonoperative 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.[1,3,6,7,18,20,27,32] 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.[2,8,9,22,23,25,26] 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 1 year.[25] 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 versus a local anesthetic alone (placebo control group) for the treatment of Morton's neuroma. Our hypothesis was that patients infiltrated with corticosteroids would experience a significant improvement in pain relief at 3- and 6-month follow-up when compared with 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.

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 weightbearing or with certain/tight footwear, 3) clinical improvement after removal of conflicting footwear or after massage, 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 or older, had failed to improve with adequate nonoperative 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 2 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; 4) patients taking anticoagulants or with an allergy or hypersensitivity to any component; and 5) patients under concomitant treatment with analgesics, anti-inflammatories, or neuromodulators for other conditions.

All patients eligible for inclusion were invited to participate in the study and were provided with a study description, including specification about the randomization process and blinding to receive 1 of the 2 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. In addition, the size was quantified in centimeters by a musculoskeletal radiologist.[4] 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 an 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 accessible only to the pharmacy department providing the medications. The researcher who performed the infiltration was different from the researcher who collected the data. Both the patients and the researcher who collected the data were blinded to treatment assigned. The pharmacy provided the syringes, which 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 was not possible because of the visible differences in the color and density of the residual liquid of the 2 compounds seen on the skin at the end of the infiltration.

All patients included in this study had 5 clinical visits scheduled. At the first clinical visit (V1), pre-infiltration study variables were collected and the first infiltration was carried out. The second visit (V2) was scheduled a week later for the second infiltration. The third visit (V3) occurred 2 weeks after the first one, when patients received the last

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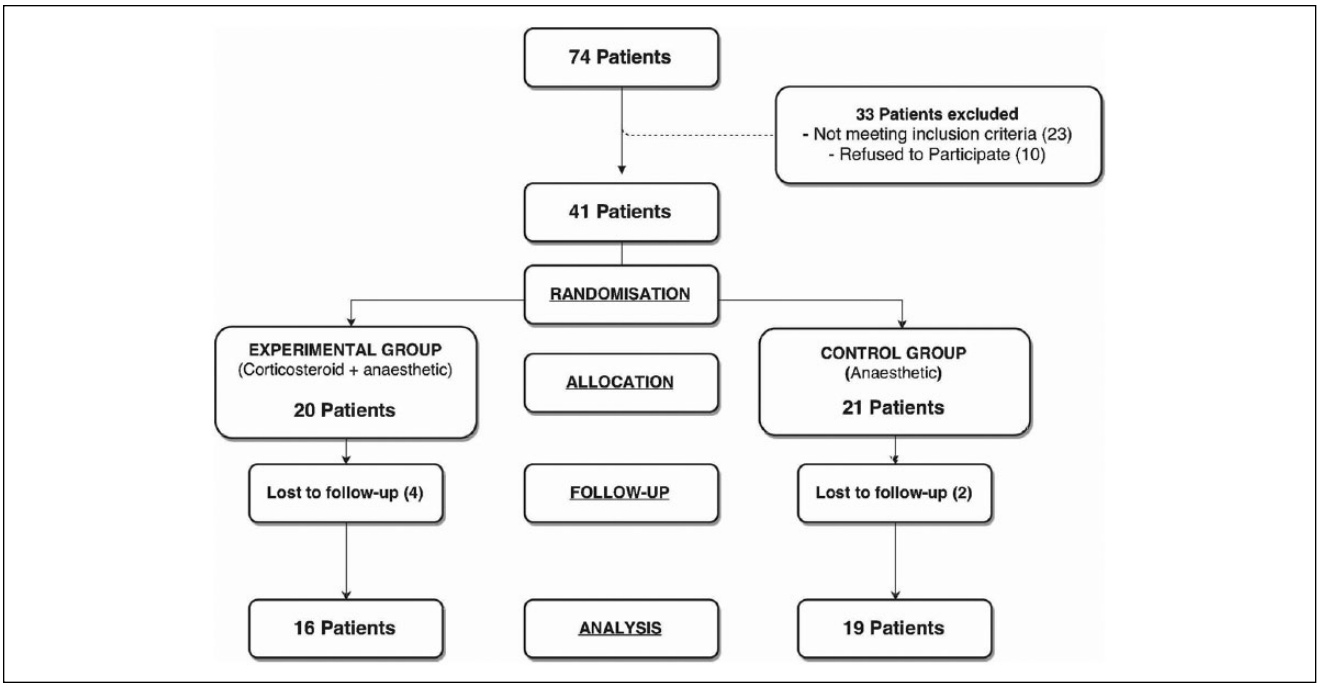


Figure 1. Flow diagram with the enrollment, randomization, follow-up, and analyzed patients.

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 2 years (January 2013 to January 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 met 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 2 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. Both groups were compared for demographic data and injury characteristics at the beginning of the study and were found to be comparable for those variables (Table 1).

Treatment Methods

The experimental group underwent 3 injections of 2 mL of a corticosteroid plus an anesthetic (1 mL mepivacaine 2% + 1 mL triamcinolone 40 mg) for each one. The control group underwent 3 injections of 2 mL of mepivacaine 2% for each patient. The 3 injections were given 1 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 injections were performed in the outpatient clinic by 2 foot and ankle specialists following the same protocol. Aseptic conditions were ensured with use of iodine and sterile latex/nitrile gloves. Then, the infiltration was performed via dorsal in the greater area of tenderness 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. Patients 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 Orthopaedic Foot & Ankle Score (AOFAS) clinical rating system test (metatarsophalangeal 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.

Table 1. Comparison of Demographic and Injury Characteristics Between the Steroid and Control Groups.

Parameter	Steroid Group (n = 16)	Control Group (n = 19)	*P* Value
Gender, n (%)	Women: 12 (75)Men: 4 (25)	Women: 17 (89)Men: 2 (11)	.379
Age, y, mean (SD)	57.7 (9.8)	60.7 (11.6)	.635
Height, cm, mean (SD)	163.6 (8.0)	160.2 (9.9)	.206
Weight, kg, mean (SD)	71.6 (13.4)	65.9 (12.2)	.235
BMI, mean (SD)	26.7 (4.3)	25.6 (3.3)	.837
Side, n (%)	Right: 10 (63)Left: 6 (37)	Right: 8 (42)Left: 11 (58)	.229
Location, n (%)	Second IM space: 6 (38)Third IM space: 10 (62)	Second IM space: 2 (11) Third IM space: 17 (89)	.105
Duration of symptoms (mo), mean (SD)	21.6 (20.8)	20.58 (14)	.756
Size (cm),[a] mean (SD)	0.8 (0.2)	0.8 (0.2)	.659
Irradiation of pain, n (%)	6 (38)	13 (68)	.067
Paresthesia, n (%)	12 (75)	14 (74)	.999
Positive Mulder's sign, n (%)	14 (87)	17 (89)	.778

[a]In the greatest diameter.
Abbreviations: BMI, body mass index; IM, intermetatarsal; SD, standard deviation.

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 30 mm 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

The comparison of VAS for pain and AOFAS between the 2 groups for each study period is shown in Table 2. The most significant VAS and AOFAS score 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 ($P = .685$). Table 4 summarizes the influence of demographic and injury characteristics on the differences in VAS and AOFAS scores between the baseline (V1) and the last follow-up at 6 months (V5). A significantly better response to the treatment relative to pain and AOFAS scores was seen in older patients ($P = .018$ for pain and $P = .002$ for AOFAS) and patients with a shorter duration of symptoms ($P = .047$ for pain and $P = .048$ for AOFAS). In addition, patients with an absence of radiating pain at the beginning of the study had better improvement in pain after 6 months ($P = .027$).

Table 2. Comparison of Visual Analog Scale (VAS) for Pain and American Orthopaedic Foot & Ankle Score (AOFAS) Between Both Groups for Each Study Period.[a]

Parameter	Steroid Group, Mean (SD)	Control Group, Mean (SD)	*P* Value
VAS			
V1	48.5 (2.2)	54.8 (2.6)	.48
V2	27.4 (2.8)	51.8 (2.1)	**.01**
V3	35.8 (2.8)	37 (2.6)	.91
V4	25.6 (2.7)	23.8 (1.5)	.64
V5	28.4 (3.3)	33.6 (3.2)	.88
AOFAS			
V1	78.6 (8.2)	73.8 (12.1)	.44
V2	84.4 (6.8)	76.7 (10.7)	**.04**
V3	82.9 (9.4)	77.6 (13.5)	.27
V4	84.6 (9.2)	83.1 (8.1)	.67
V5	84.5 (13.8)	81.2 (11.1)	.26

Abbreviations: V1, first visit; V2, second visit; V3, third visit; V4, fourth visit; V5, fifth visit.
[a]Bold values are significant.

Table 3. Comparison of Intra - and Inter-group Differences in Visual Analog Scale (VAS) for Pain and American Orthopaedic Foot & Ankle Score (AOFAS) Between Baseline (V1) and the Rest of the Study Periods.[a]

	V2-V1	*P* Value	V3-V1	*P* Value	V4-V1	*P* Value	V5-V1	*P* Value
VAS								
Steroid group, mean (SD)	−21.1 (26.7)	**.004**	−12.66 (20.1)	**.030**	−22.8 (28.7)	**.006**	−18.18 (23.6)	**.012**
Control group, mean (SD)	−3.03 (28.7)	.777	−17.79 (37.4)	.056	−28.56 (30.1)	**.002**	−16.38 (40.9)	.163
Intergroup difference (*P* value)	**.048**		.806		.851		.728	
AOFAS								
Steroid group, mean (SD)	5.81 (6.2)	**.004**	4.31 (8.6)	.068	6.0 (8.7)	**.021**	5.14 (12.9)	.126
Control group, mean (SD)	2.89 (12.9)	.265	3.73 (12.8)	.120	7.88 (13.6)	**.024**	5.82 (16.4)	.147
Intergroup difference (*P* value)	.257		.961		.721		.830	

[a]Bold values are significant.

Table 4. Influence of Demographic and Injury Characteristics on the Visual Analog Scale (VAS) for Pain and American Orthopaedic Foot & Ankle Score (AOFAS) Differences Between the Baseline (V1) and Last Follow-up at 6 Months (V5).[a]

		VAS V5-V1		AOFAS V5-V1	
Parameter		CC (*r*)	*P* Value	CC (*r*)	*P* Value
Age		**–0.43**	**.018**	**0.53**	**.002**
BMI		−0.1	.592	−0.07	.689
Size		0.08	.659	−0.19	.299
Duration of symptoms		**0.23**	**.047**	**−0.26**	**.048**
		Mean (SD)	***P* Value**	**Mean (SD)**	***P* Value**
Gender	Female	−1.19 (3.2)	.146	3.84 (12.8)	.515
	Male	−3.82 (3.3)		12.5 (20.6)	
Side	Right	−2.44 (3.3)	.371	5.29 (13.8)	.842
	Left	−0.9 (3.4)		5.78 (16.2)	
Location	Second IMS	−1.83 (2.5)	.944	5.13 (15.7)	.892
	Third IMS	−1.68 (3.7)		5.65 (14.7)	
Paresthesia	Yes	−1.36 (3.1)	.205	6.6 (14.7)	.526
	No	−2.7 (3.9)		2.38 (15)	
Radiating	Yes	−0.55 (3.2)	**.027**	3.29 (16.7)	.330
	No	−3.25 (3)		8.21 (11.7)	
Mulder	Positive	−1.54 (3)	.053	4.52 (13.3)	.425
	Negative	−5.37 (2.9)		17.33 (26.1)	

Abbreviations: BMI, body mass index; CC, correlation coefficient; IMS, intermetatarsal space; SD, standard deviation.
[a]Bold values are significant.

There were no statistically significant differences in the degree of satisfaction at 6 months between both groups ($P = .744$). In the steroid group, 6 patients (37.5%) were satisfied, 4 (25%) were satisfied with minor reservations, 3 (19%) were satisfied with great reservations, and 2 (12.5%) were dissatisfied. One patient (6%) said "I wish I had never undergone the infiltration." In the control group, 6 patients (32%) were satisfied, 5 (26%) were satisfied with minor reservations, 3 (16%) were satisfied with great reservations, and 5 (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, 9 patients in the steroid group (56%) and 7 patients in the control group (37%) reached that improvement at 6 months. At the end of the study, there were 17 (48.5%) patients requesting surgical excision of the neuroma: 7 (44%) in the steroid group and 10 (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.[10,22,23,25,26] Several studies have observed that the benefits of corticosteroid injections are only immediate or short term.[10,22,23,25,26] The present study demonstrated that the steroid group maintained a significant intragroup improvement in the VAS over the 6 months in comparison to the control group, where the intragroup improvement in terms of pain was significant only at 3 months. The difference between the initial and final follow-up was statistically significant only in the steroid group ($P = .012$). Nevertheless, the significant intergroup differences were only in the first week. This means that the corticosteroid injections had a beneficial immediate effect over the placebo. However, this beneficial effect on pain was diminished after a short period of time. Although the greatest improvement occurred between baseline and 3 months, improvement in the VAS for pain at 6 months was still clinically relevant, as the reduction was superior to 33% from baseline.[15,28] In contrast, AOFAS showed an isolated significant intragroup improvement at 3 months in both groups (with a modest intragroup improvement maintained over time in both groups) with no intergroup statistical differences. Despite the relevant intragroup improvements, it did not appear to influence final patient outcomes and surgical rates between groups.

Thomson et al[25] observed significantly better patient global assessment of foot health and some of the parameters of the Manchester Foot Pain and Disability Schedule and the Multidimensional Affect and Pain Survey at 1 and 3 months after corticosteroid and anesthetic injection compared to an anesthetic alone. Nevertheless, significant differences were not maintained at 1 year after treatment. 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 3 months) with no differences between them at 6 months. The greatest improvement in pain and AOFAS was seen at 3 months, but then a slight non–clinically relevant decrease in both values was observed at 6 months. This is consistent with previous findings of positive results with infiltrations in the short term, worsening later with virtually no effect at 1 year of infiltration.[22]

The significant and long-lasting improvement in pain and the AOFAS, as well as satisfaction, demonstrated 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.[11,19] This seems particularly true for satisfaction, as patients receiving multiple infiltrations seem to show higher satisfaction values compared to those receiving only 1 injection.[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 observe 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 negative correlation with the differential (V5-V1) AOFAS may have indicated 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.[2] They found that patients with symptoms of less than 1 year's duration appeared to do better than those with symptoms of more than 1 year's duration. 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, and size and location of the neuroma on the outcomes of corticosteroid 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[24] reported that excision of larger lesions led to higher cure rates than did the removal of smaller lesions. On the other hand, Biasca et al[3] reported that lesions of less than 5 mm in size that produced metatarsalgia were treated successfully with neurolysis and division of the intermetatarsal ligament, whereas larger lesions were treated with excision. 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 a radiologist under 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 compared to blind injections. However, this technique is operator dependent and does not show the reality of most clinical practices, where a radiologist may not be easily available in the outpatient clinic. This makes for the current practice of performing a dorsal blind injection without the assistance of ultrasound 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 had 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 was effective for the treatment of Morton's neuroma. A prolongation of the study was discussed, but it was finally decided not to prolong the follow-up given the results obtained at 6 months, which demonstrated stabilization of the improvements as previously found by other authors with a 1-year follow-up period.[25] Second, the physicians performing the injections were not blinded to the treatment group, which could unintentionally influence the outcomes. However, care was taken not to break patient blinding and to not affect their perception or create any type of influence on the outcomes. Third, performing multiple injections increased the risk of losing patient blinding, but we are unaware of any patients discovering which group they had been allocated to before the completion of the study. Fourth, no objective outcomes were obtained after the treatment (ie, 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 has not been confirmed, but the subjective component (pain) of this score was evaluated by Ibrahim et al.[13] 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 methodology of the study makes conclusions potentially more robust compared to previous studies.[5,10,12,22,23]

Conclusion

The injection of a corticosteroid plus a local anesthetic was 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 were 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.

Declaration of Conflicting Interests

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