Title

Infiltrative treatment of Morton's neuroma: A systematic review.

Abstract

Background: Morton's neuroma (MN) is one of the most frequent neurological pathologies in feet, affecting approximately 4% of the general population. The treatment of MN can be surgical, conservative, and infiltrative, with different substances used in the injections for MN, as steroids, sclerosing solutions, and others. This review aims to evaluate the efficacy of current infiltrative therapy for Morton's neuroma and, additionally, to define adverse effects of this therapy.

Material and Methods: A literature search was performed in PubMed, Embase, CINHAL, Epistemonikos, Web of Science (WOS), SPORTSDiscus and Cochrane Library. This search involved the application of all types of infiltrative treatment applicable to MN. The search was limited to original data describing clinical outcomes and pain using the Visual Analogue pain Scale (VAS) or the Johnson Satisfaction Scale, between February and June 2023.

Results: Twelve manuscripts were selected (6 randomized controlled trials and 6 longitudinal observational studies) involving 1,438 patients. Capsaicin was reported to produce a VAS score reduction of 51.8%. Corticosteroids also reported a high level of efficacy. Alcohol and Hyaluronic Acid injections are well tolerated, but the effects of their application need further research. There were no serious adverse events.

Conclusions: Corticosteroids, sclerosant injections, hyaluronic acid and capsaicin have been shown to be effective in reducing the pain related to MN.

Key words

Morton’s Neuroma, Injection, corticosteroid, capsaicin, hyaluronic acid, alcohol.

Key practice points

Triamcinolone and methylprednisolone are effective in reducing the pain associated with Morton's neuroma.

Corticosteroids have low risk of complications, such as skin depigmentation and atrophy of the plantar fat pad.

Sclerosant injections, hyaluronic acid and capsaicin still lack sufficient evidence of effectiveness, although none was associated with severe adverse effects.

1. Introduction

Morton's neuroma (MN) is a non-neoplastic fusiform enlargement of a medial or lateral plantar nerve branch, preferentially affecting the female sex, with a 4:1 ratio (Quinn et al., 2000), bilaterally in 21% of cases, and may occur in the third intermetatarsal space (66%), second (32%) or fourth (2%) (Kasparek & Schneider, 2013). Patients usually have forefoot pain that may be associated with burning, tingling or numbness, originating in the region of the metatarsal heads and radiating into the toes (Quinn et al., 2000). The pain often increases with walking and wearing narrow-toed shoes and is relieved with rest.

Many interventions have been used to treat Morton's neuromas. Primarily, a non-surgical option is preferred. Current conservative treatments include adapted footwear, insoles, physical therapy, injections, cryotherapy, radiofrequency ablation, and shock wave therapy. Surgical treatment offers good to excellent results in 80% of patients (Gougoulias et al., 2019), but it is indicated after conservative treatment has failed.

Injection therapy may provide a solution before surgery is considered, although there are different therapeutic approaches. In addition, the joint use of ultrasound guidance increases the efficacy of injections because it facilitates the precise placement and actual timing of the needle in the MN complex, avoiding other soft tissue structures (Ruiz Santiago et al., 2019). Recommendations for different drug substances to be injected directly into the MN can be found in the literature. Some of the most frequent are: Corticosteroids, which induce atrophy of the tissue of the intermetatarsal space and, therefore, decrease compression and inflammation of the neuroma (Read et al., 1999); Sclerosing agents, such as alcohol (Pasquali et al., 2015), which when infiltrated in the specific area cause a controlled inflammatory reaction leading to the formation of fibrous tissue and the obliteration of blood vessels; Capsaicin, which brings about a loss of nociceptor afferents (Urits et al., 2020); and Hyaluronic acid, a glycosaminoglycan with anti-inflammatory properties and which promotes cell proliferation, so it could have positive effects in the treatment of MN through injection (Lee et al., 2018; Ozgenel, 2003; Wang et al., 1998).

However, these substances are not free of complications or adverse effects when injected as MN treatment. It has been described that multiple corticosteroid injections may carry the risks of plantar fat pad atrophy, dermal thinning and depigmentation (Rao et al., 2014). As for sclerosing agents, a major skin complication was reported as deep necrosis of skin and subcutaneous tissue after the injection of therapeutic alcohol solution (Ortu et al., 2022). With capsaicin injected directly into the neuroma patients usually experience localized pain that disappears after several hours (Urits et al., 2020).

Given the variety of therapeutic alternatives available to treat MN, it can be difficult to determine which is the most appropriate option for each patient, as scientific evidence may be limited in some cases to support its efficacy and safety. Therefore, this

systematic review aims to evaluate the efficacy of current infiltrative therapy for MN. In the authors' opinion, this review is important since it will provide useful information to healthcare professionals that will help them make decisions about the choice of drug to use in injection therapy for the adequate treatment of patients with MN.

2. Methods

A systematic review of the literature was carried out, following the guidelines of the PRISMA statement. This review was registered in PROSPERO prior to its completion, with ID number: CRD42023407842.

In order to answer the main question, it was broken down into the following sections (PICOs):

Participants: adult patients of both sexes with Morton's neuroma.

Intervention: intralesional injection of drugs.

Comparison: any other treatment and placebos.

Outcomes: pain relief and, additionally, occurrence of adverse effects.

Study Design: randomized clinical trials and longitudinal observational studies pre-post intervention.

2.1. Search methods for study identification

Electronic search:

To conduct the systematic review, an electronic literature search was performed in the databases: PubMed, Embase, CINHAL, Epistemonikos, Web of Science (WOS), SPORTSDiscus and Cochrane Library between February and June 2023. The following search strategy was used, with no limits on publication dates:

(Morton neur* OR interdigital neur*) AND (therap* OR injection OR conservative treatment) AND (sclerosing agent OR sclerosing solution OR sclerotherapy OR capsaicin OR steroid OR corticosteroid OR methylprednisolone OR lidocaine OR mepivacaine OR bupivacaine OR anesthesia OR botulinum toxin OR carbamazepine OR betamethasone OR hyaluronic acid OR collagen OR platelet rich plasma OR cortisone OR prednisone OR triamcinolone acetonide OR mesenchymal stem cells).

The electronic search was supplemented by reviewing reference lists of articles included in our review. However, none of these was selected to participate in the systematic review as they did not fit the inclusion criteria but were chosen as an aid in constructing the introduction and discussion.

2.2.Selection of studies

Studies involving treatment of MN by injection were included for a full-text review, those that reported only results, and those reporting results and describing complications arising from infiltrative treatment of MN.

Inclusion criteria

We have included randomized controlled clinical trials and pre-post longitudinal observational studies in patients diagnosed with MN, as the authors also wanted to estimate the effectiveness of the intervention under conditions of routine clinical practice, which may be different from those of clinical trials.

Exclusion criteria

Animal studies, case reports and studies that did not differentiate MN from other forms of metatarsalgia. Articles that did not quantify pain reduction with VAS (Visual Analogue Scale) or Johnson's satisfaction scale were excluded.

2.3. Data Collection

Two authors (MOMS and SPTV) independently carried out the search and selection process. Both reviewers performed an initial screening by reading the title and abstract of each of the articles to assess whether they met the previously defined inclusion criteria. After this process, the results of both reviewers were pooled, and the full text of the documents was read. There were discrepancies between the two authors in 4 articles. At this point, a third author (PVMM) intervened and, after reading the full text of the conflicting documents and according to the previously established selection criteria, decided that they should not be included. The procedure for the selection of articles is summarized in figure 1.

To facilitate the study selection process and data extraction, each reviewer was provided with an Excel sheet. This sheet recorded the studies included, those excluded and the reason for exclusion, primary outcomes (pain) and secondary outcomes (adverse effects). These data were collected by coding the criteria to be evaluated. The primary outcome sought was treatment effectiveness, based on patient-referred pain. The secondary outcomes were the adverse effects that the patients presented because of the injections.

2.5. Variables measured

The following parameters were measured:

Effectiveness, referring to pain reduction. Mainly the visual analog pain scale (VAS) was used. The difference in the VAS score between baseline (before the patient underwent infiltrative treatment) and the end of follow-up was quantified. In one of the studies

included in the review, effectiveness was quantified by "level of satisfaction"; which was classified into 3 categories: totally satisfied, satisfied with mild discomfort, and dissatisfied. Another study used the Numerical Pain Rating Scale (NPRS-11), a segmented numerical version of the visual analog scale (VAS) in which the respondent selects a whole number (0-10) that best reflects the intensity of his or her pain.

Adverse effects associated with treatment. It was determined whether adverse effects were reported, what they were and how long they lasted.

2.6. Effect measurements and data synthesis

Effectiveness and adverse effects data were tabulated to observe the prevalence rates of each type of complication. Effectiveness was recorded in terms of pain reduction, measured with whatever scale or tool used by the authors to register perceived pain or global satisfaction (when a component of pain was included in the latter). Any post-injection symptoms reported by the participants, or any local complications observed by the authors, (i.e., numbness, local pain, swelling, skin depigmentation, etc) were registered as adverse effects. Missing data were noted as such.

2.7. Bias risk assessment

The following methods were used to assess the quality of the studies:

The Risk of Bias 2 (RoB 2) tool was used by means of the RevMan software, to assess each of the bias items of the randomized controlled studies included in the present review. This tool consists of items structured into a fixed set of domains of bias (selection, performance, detection, attrition, reporting and other bias). A judgement about the risk of

bias derived from each domain is proposed based on answers to signaling questions. Those judgements may be 'low' or 'high' risk of bias, or 'some concerns'.

The Newcastle-Ottawa Scale is a valid and reliable tool for the assessment of the quality of case-control and cohort studies. In this review, none of the observational included studies presented more than one group of participants, that is, none presented a control group or a non-exposed cohort. For this reason, the risk of bias of observational included studies was evaluated with an adapted version of the Newcastle-Ottawa Scale which has been previously used in other systematic reviews to evaluate the quality of any observational design (Bawor et al., 2015; Martinez-Calderon et al., 2018). This scale consists of 7 items grouped into 4 domains (selection bias, performance bias, detection bias and information bias). For each item, a punctuation from 0 to 3 was assigned, where 0 = Definitely no; 1 = Mostly no; 2 = Mostly yes; 3 = Definitely yes

3. Results

A total of 431 manuscripts were initially identified from PubMed, Embase, CINHAL, WOS, Epistemonikos, SPORT Discuss and Cochrane Library searches in June 2023. After reading the titles and eliminating duplicates, 373 were excluded, so 58 papers were selected for a full reading. Thirty-five articles were excluded because they did not provide relevant information related to the objectives of the review, and of the remaining 22, 10 were excluded because they did not meet the selection criteria (figure 1).

Finally, 12 articles were included, of which 6 were randomized controlled clinical trials and 6 were longitudinal observational studies without a comparison group, which together reported the results of a total of 1438 patients. The information related to symptoms duration before the injection was only available in six studies: Campbell et al (2016) reported that their patients had to have pain related to MN for a minimum period

196 of one week, 2 months was the minimum duration in Lee et al's study (2018) and 6
197 months in other 4 studies (Mahadevan et al., 2016; Pasquali et al., 2015; Ruiz Santiago
198 et al., 2019; Thomson et al., 2013). Only five of the reviewed articles specified that
199 patients with concomitant symptoms from other foot pathologies or severe forefoot
200 deformities were excluded (Campbell et al., 2016; Lee et al., 2018; Lizano-Díez et al.,
201 2017; Mahadevan et al., 2016; Park et al., 2018). This information was not available in
202 the remaining papers. All reviewed studies except that by Saygi et al (2005) reported
203 some kind of local complications or other adverse effects. The characteristics of the
204 included studies, and detailed information about the results obtained, as well as about the
205 adverse effects observed, are shown in tables 1 and 2.
206
207 *3.1. Randomized controlled clinical trials*
208 Six RCTs were analyzed. Of these 6 studies, 5 evaluated the effectiveness of
209 corticosteroid injections, and one reported the efficacy of capsaicin injected into the MN.
210 The capsaicin injections achieved a 58.1% reduction in pain at the end of their follow-up
211 periods compared to the placebo group, in which the reduction was 47.6% (Campbell
212 et al., 2016). The use of steroids decreased pain an average of 52.6% in the participants
213 of the experimental groups, compared to an average of 33.3% in participants who did not
214 received treatment (Lizano-Díez et al., 2017; Saygi et al., 2005; Thomson et al., 2013).
215 Some studies compared the effectiveness of ultrasound image guidance versus no
216 guidance treating patients with corticosteroids in both groups (Mahadevan et al., 2016;
217 Ruiz Santiago et al., 2019). In these studies, it was observed a mean pain reduction of
218 nearly 40% (higher with US guidance - 60.7% to 70.3%), which also indicates that
219 triamcinolone (the steroid employed in these studies) was effective in decreasing pain.

The risk of bias of the included randomized clinical trials is summarized in figures 2 and 3. As can be seen, these are articles that have mostly shown a low risk of bias. However, the RCT by Lizano-Díez et al (2017) showed a high risk of bias in the blinding of participants and staff. The RCT of Ruiz-Santiago et al (2019) presented a high risk of bias in the concealment of information. The studies by Saygi et al (2005) and Thomson et al (2013) showed uncertain risk of bias in conduct and detection. It should be noted that there were studies, such as those by Campbell et al (2016) and Mahadevan et al (2016) that presented a low risk of bias in all RevMan scores, which improves the quality of the evidence collected, increasing confidence in the results and minimizing the probability of obtaining incorrect or biased conclusions.

3.2. Longitudinal observational studies

A total of 6 studies were included, three of them addressed MN treatment by sclerosant injections, two by corticosteroids, and only one used hyaluronic acid as therapy.

The alcohol injections achieved a 41.6% reduction in pain at the end of their follow-up periods (Espinosa et al., 2011; Pasquali et al., 2015). However, Espinosa et al (2011) sustained that alcohol sclerosing therapy was not an effective treatment for nonoperative management of MN. The use of corticosteroids showed a greater decrease in pain, with a mean reduction of 59% in the participants of the two studies in which were used (Park et al., 2018; Rao et al., 2014). Hyaluronic acid injections have also been shown to be effective in reducing pain, with pain levels decreasing by 68.5% (Lee et al., 2018).

The risk of bias of longitudinal studies, assessed with the modified NOS scale,(Martinez-Calderon et al., 2018) is summarized in table 3. As can be seen, these articles showed satisfactory or average scores for risk of bias, with the exception of the

study by Rao et al. which only obtained 3 points in the sum of the risk of bias items (Rao et al., 2014).

4. Discussion

The main objective of this systematic review was to determine the efficacy of infiltrations in Morton's neuroma and, secondarily, to define the adverse effects derived from them.

For the evaluation of pain intensity and pain relief, the visual analog scale (VAS) was used. Kelly et al (1998) established that the minimum clinically significant difference in 100 mm VAS pain scores was 9 mm (95% CI, 6-13 mm). Differences less than this amount, even if statistically significant, are unlikely to be of clinical significance. Farrar et al (2000) stated that a good cut-off point to establish the significant clinical relevance of the VAS scale would be a 33% decrease in the score at the end of the follow-up with respect to the score before starting treatment. According to this, it seems that corticosteroids represent the injection therapy that provide the best results in pain reduction, follow by hyaluronic acid, capsaicin, and alcohol.

Triamcinolone seems to have a highly positive effect in terms of pain reduction, according to the studies reviewed. Lizano-Díez et al (2017) observed 41.4% decrease in the VAS scale score after 6 months, Ruiz-Santiago et al (2019) obtained 60.7% of pain reduction after 3 years, and Mahadevan et al (2016) achieved 70.3% decrease in the VAS scale score after 12 months. The adverse effects that occurred with triamcinolone were skin depigmentation at the injection site and/or atrophy of the plantar fat pad. These effects appeared in a very low percentage of patients and no additional actions were required. The participants did not develop more serious complications, so this drug provides a high level of safety.

Methylprednisolone also showed a significant improvement in pain, although with lower figures compared to triamcinolone. Thompson et al (2017) observed 38% decrease in the VAS scale score after 3 months, and Rao et al (2014) obtained 51.8% of pain reduction after 2 months. Saygi et al (2005) also observed that in the short term, methylprednisolone injections were more effective in reducing pain than foot orthoses (82% and 63% satisfaction, respectively), but after a period of one year, orthopedic treatment was just as effective. Regarding adverse effects, the results were very similar to triamcinolone, i.e., local skin hypopigmentation and atrophy of the plantar fat pad, although several patients experienced numbness, swelling and pain that were resolved in less than 48h (Rao et al., 2014). Saygi et al (2005) reported no adverse effects, and suggested that methylprednisolone, like triamcinolone, provides a high level of safety.

Park et al (2018) evaluated the effectiveness of dexamethasone. They reported a large decrease in the short-term VAS score (66.3% after 6 months), especially in neuromas smaller than 6.3 mm in size, and no adverse effects were reported. Other authors have also studied the relationship between corticosteroid injection and neuroma size, showing that the effectiveness of injection appeared to be greater and longer lasting for lesions smaller than 5 mm (Makki et al., 2012).

Regarding sclerosing agents, alcoholic neurolysis has been widely used in the treatment of other neuropathic pain conditions caused by peripheral nerves, such as the lateral femoral cutaneous nerve and intercostal nerves (Ahmed et al., 2016). In the study by Pasquali et al (2015) 50% alcohol injection was well tolerated by all patients with MN and there were no major complications in any patient. After 12 months, the VAS score was significantly reduced by more than 50 mm. The authors reported that histological examination of surgically removed neuromas suggested that injected neuromas showed reduced cellularity and intraneural fibrosis (Pasquali et al., 2015). These findings suggest

some affinity between alcohol and nerve cells, which respond by degenerating into sclerotic tissue. There is no conclusive opinion in the literature on the optimal alcohol concentration for injections. However, Santos et al (2018) report that adverse injection events occur with alcohol concentrations between 30% and 50%. Ortu et al (2022) stated that there was no relationship between the severity of complications and the amount of alcohol injected. In most cases in their study the injection caused a momentary exacerbation of pain at the injection site and a "pebble sensation" between the third and fourth metatarsal heads, which spontaneously regressed within a few hours. However, in a small number of patients, this was affected by a "major" complication.

The only study included in this review that treated MN with hyaluronic acid injections was that of Lee et al (2018), in which pain relief for at least 12 months in patients with MN was observed. The effectiveness at the 2-month follow-up was very high. HA did not influence the initial numbness associated with neuromas. It is possible that hyaluronic acid decreased inflammation, scar formation, and adhesion around the neuromas. Only in some cases there were temporary discomforts for 1 or 2 days such as pain and hematomas (although the latter could have been due to incidences in the puncture procedure, not attributable to HA). There were no long-term complications for at least 12 months after the injections (Lee et al., 2018). Although it is used in other specialties of medicine such as ophthalmology, plastic surgery, or orthopedics, with few or no adverse effects, the authors cannot strongly recommend this treatment as there is still little evidence on the effectiveness of HA in the treatment of MN.

Capsaicin has been shown to be effective when administered topically to treat neuropathic pain associated with postherpetic neuralgia and diabetic neuropathy (Derry et al., 2017). It is now known that high-dose capsaicin (20 mg/20 ml) applied topically to the skin (patches) provides rapid and sustained pain relief in patients with various

peripheral neuropathic disease conditions, and significantly reduces the prescription of concomitant analgesic medication. The main adverse effects reported (local reactions at the application site such as pain and erythema) were transient (Alcántara Montero et al., 2019). The same adverse effects were observed in the study evaluating the effectiveness of capsaicin injected into the MN (Campbell et al., 2016). The results showed a significant decrease in pain with a single dose. Reductions in oral analgesic use were also observed in the capsaicin-treated group. Although these findings suggest that capsaicin injection is an effective and safe treatment option for patients with MN, it is still unknown how dosing in a neuroma corresponds to dosing in the skin, so this aspect deserves consideration in future studies before a strong recommendation.

Limitations

One of the main limitations of this review is the inclusion of longitudinal observational studies, which have a higher risk of bias, and from which less evidence is obtained, since their results are not compared with those of a control group, and patients who had been previously treated with other conservative therapies are included. In addition, some of the RTCs also had high risk of bias, so the results of this review should be interpreted with caution.

The diagnosis of MN was not confirmed by histological examination in all the patients, but the overall accuracy of the combined clinical and imaging diagnosis is reported to be remarkably high (>95%).

Another limitation is that most of the included studies had a 12-month follow-up, so it cannot be assured that the effectiveness is the same after a longer time.

It should also be noted that not all the studies performed the same number of injections, so it is not possible to draw firm conclusions regarding doses and treatment regimens.

And finally, the studies that have included neuroma size as a variable seem to have observed that in larger neuromas the success of the injections is less assured, so we cannot rule out that the good results observed in many of the included studies are related to a smaller size of the MN.

5. Conclusions

In summary, this review indicates that corticosteroids, especially triamcinolone and methylprednisolone, are effective in reducing the pain associated with Morton's neuroma. Both have low risk of complications, such as skin depigmentation and atrophy of the plantar fat pad. Overall, corticosteroids show effectiveness and safety, but more studies are needed to evaluate the long-term effectiveness of corticosteroid injections in the treatment of MN.

Although sclerosant injections, hyaluronic acid and capsaicin have been shown to be effective in the consulted studies, low evidence still exists due to the small number of articles found; further research is needed to achieve more conclusive recommendations. None of these substances were associated with serious adverse effects in the included studies.

Declaration of Generative AI and AI-assisted technologies in the writing process

None

Declaration of interest

None

6. References

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Figure captions

Figure 1. Flow chart showing the stages of the selection process of the studies included in the review.

Figure 2. Risk of bias graph: judgments on each risk of bias item for each RCT included in the review (Created with RevMan).

Figure 3. Summary of risk of bias: judgments on each risk of bias item for each RCT included in the review. (Created with RevMan).