Introduction

Morton’s neuroma is a well-known cause of forefoot pain and is considered a degenerative neuropathy featuring fibrosis of the common interdigital nerve of the second or third intermetatarsal space (1-2).

It is one of the most common entrapment syndromes, secondary to nerve compression under the transverse metatarsal ligament, chronic traction damage, intermetatarsal bursitis related to an inflammatory environment. Repetitive microtraumas and ischemic factors leads to a proliferative fibrosis of perineural tissue (3-6).

Patients typically report forefoot pain, burning and numbness between the toes. Activities such as walking, standing or wearing tight shoes exacerbate the symptoms (7).

The diagnosis of Morton’s neuroma is principally based on each patient’s history and clinical findings, and is validated using imaging studies: ultrasonography and magnetic resonance.

The recommended treatment of Morton’s neuroma is initially conservative. If this fails, it progresses to infiltrations and then surgery.

Infiltrative treatment includes injections of local anesthetic, steroids, alcohol, other sclerosing agents such as phenol, capsaicin, botulinum toxin A, hyaluronic acid. It is also suggested the use of radiofrequency ablation, which is included in the review because even if they are not infiltrations they are performed by a needle.

The aim of this review is to compare the outcome of different types of Morton’s neuroma injections.

Primary outcome defines which treatment provides the best results in terms of patient’s satisfaction and pain relief. Since recurrence is a possible event, the length of follow-up is an important variable to identify durable results.
Secondary outcome defines the evaluation of complications such as post-procedural pain, allergic reactions, hematomas.

**Methods**

**Literature search**

The present review was conducted according to the PRISMA guidelines (preferred reporting items for systematic reviews and meta-analyses) (8).

A literature search was conducted on various electronic databases, including PubMed, MedLine, Cochrane Library, from year 1976 to July 2021, using the following search: Morton’s neuroma injection, Morton’s neuroma treatment, Morton’s neuroma physical therapy, Morton’s neuroma alcohol, Morton’s neuroma corticosteroid, Morton’s neuroma hyaluronic acid, Morton’s neuroma conservative.

**Including criteria**

We have included prospective and retrospective case series, and randomized controlled trials of infiltrative treatments in patients with primary diagnosis of Morton’s neuroma.

**Exclusion criteria**

The following exclusion criteria were used:

Papers in languages other than English, animal studies, case reports, studies that did not differentiate Morton’s neuroma from other forms of metatarsalgia, or in which the results were cumulative. Studies including stump neuromas, or neuroma recurrence as first treatment were also excluded. Duplicate papers, studies where data extraction was not possible, papers that had an unclear description of population were excluded as well.

**Papers selection and data extraction**

The procedure for papers selection is described in the flow chart in Figure 1.

The extraction of the data has been performed by two authors, independently and without cases of disagreements.

Information extracted from every included study related to demographic data (number of patients, affected foot, mean age, gender . . .) and clinical data (type of treatment, range of follow-up, clinical outcomes, complications . . .) are summarized in table 1 and 2.
Table 1. Design and demographic characteristics of all included studies (NR = not reported/ not clear)

| Author                        | Year | Location               | Study Period | Intervention                        | Study Type                                      | Gender   | Mean Age |
|-------------------------------|------|------------------------|--------------|-------------------------------------|------------------------------------------------|----------|----------|
| - Thomson CE (9)              | 2013 | Edinburgh, Scotland    | 2005–2006    | Corticosteroid injection            | Patient blinded randomized trial                 | 85% f, 15% m | 53 years |
| - Markovic M (10)             | 2008 | Sydney, Australia      | 2002–2003    | Corticosteroid injection            | Prospective case series                          | 80% f, 20% m | 54 years |
| - Park YH (11)                | 2017 | Seoul-Ansan, Korea     | 2010–2016    | Corticosteroid injection            | Retrospective case series                        | 76% f, 24% m | 56.3 years |
| - Saygi B (12)                | 2005 | Istanbul, Turkey       | NR           | Corticosteroid injection            | Randomized                                      | 87% f, 13% m | 51.9 years |
| - Ruiz Santiago F (13)        | 2019 | Granada, Spain         | NR           | Corticosteroid injection            | Evaluator-blinded randomized trial               | 89% f, 11% m | 52.2 years |
| - Lizano-Diez X (14)          | 2017 | Barcelona, Spain       | 2013–2015    | Corticosteroid injection            | Prospective, double blinded, randomized, placebo controlled | 75% f, 25% m | 57.7 years |
| - Hau MYT (15)                | 2021 | Leicester-Reading, UK  | 2012–2014    | Corticosteroid injection            | Prospective randomized                           | 68% f, 32% m | 62.6 |
| - Makki D (16)                | 2012 | Leytonstone-London, UK | NR           | Corticosteroid injection            | Prospective comparative                          | 62% f, 38% m | 31.7 years |
| - Mahadevan D (17)            | 2016 | Leicester, UK          | 2012–2014    | Corticosteroid injection            | Double blind randomized controlled               | 73% f, 27% m | 57.8 years |
| - Mahadevan D (18)            | 2015 | Leicester, UK          | 2009–2012    | Corticosteroid injection            | Retrospective case series                        | 79% f, 21% m | 55.4 years |
| - Samaila (19)                | 2020 | Verona, Italy          | 2000–2016    | Phenol injection                    | Retrospective case series                        | 80.9% f, 19.1% m | 54.4 years |
| - Pasquali C (20)             | 2014 | Luino-Varese-Abano, Italy | 2001–2012 | Alcohol (50%) injection            | Retrospective case series                        | 91.3% f, 8.7% m | 57 years |
| - Perini L (21)               | 2016 | Abano-Verona, Italy    | 2010–2011    | Alcohol (50%) injection            | Retrospective case series                        | 85% f, 15% m | 55.8 years |
| - Pabinger C (22)             | 2020 | Innsbruck-Graz, Austria | 2012       | Alcohol (70%) injection            | Prospective case series                          | 73% f, 23% m | 53 years |

(Continued)
| Author        | Year | Location                  | Study Period | Intervention                     | Study Type                | Gender         | Mean Age |
|---------------|------|----------------------------|--------------|----------------------------------|---------------------------|----------------|----------|
| Hughes RJ     | 2007 | Middlesex, UK              | 2004–2005    | Alcohol (20%) injection Ultrasound guided | Prospective case series  | 83% f,          | 53.8 years |
| Gurdezi S     | 2013 | Kingstone upon Thames, UK  | 2004–2007    | Alcohol (20%) injection Ultrasound guided | Prospective case series  | 87% f, 13% m  | 53.5 years |
| Lorenzon P    | 2018 | Cittadella, Italy          | 2012–2014    | Alcohol (30%) injection Ultrasound guided | Retrospective case series | 85% f, 15% m  | 56.5 years |
| Fanucci E     | 2004 | Rome, Italy                | 1999–2001    | Alcohol (30%) injection Ultrasound guided | Prospective case series  | 83% f, 17% m  | 48 years  |
| Musson RE     | 2012 | Oxford, UK                 | 2008–2008    | Alcohol (20%) injection Ultrasound guided | Retrospective case series | 88% f, 12% m  | 57.5 years |
| Mozena JD     | 2007 | Portland, USA              | 2003–2004    | Alcohol (4%) injection Ultrasound guided | Retrospective case series | 62% f, 38% m  | 49.8 years |
| Campbell CM   | 2016 | Baltimore, USA             | NR           | Capsaicin injection not ultrasound guided | Randomized double blind placebo controlled | 83% f, 17% m  | 52.8 years |
| Lee K         | 2018 | Gyunggi-Seoul-Gangwon, Korea | NR           | Hyaluronic acid perineural injection Ultrasound guided | Retrospective case series | 90% f, 10% m  | 48 years  |
| Shah R        | 2019 | Birmingham, UK             | NR           | Radiofrequency Ultrasound guided | Prospective case series  | 78% f, 22% m  | 57 years  |
| Connors JC    | 2020 | Independence-Denver, USA   | 2010–2012    | Radiofrequency Electrostimulation guidance | Prospective case series  | 78% f, 22% m  | Not specified |
| Climent JM    | 2013 | Alicante - Yecla – Torrevieja, Spain | NR           | botulinum toxin A injection | Prospective case series  | 41.2% f, 58.8% m | 58.2 years |

Table 1. design and demographic characteristics of all included studies (NR = not reported/not clear) (Continued)
Table 2. clinical features of all included studies (NR = not reported/ not clear, SD = Standard Deviation)

| Author                  | Assessment method | Intervention                | Number of Patients - Number of Feet (if different) | Duration of Follow-up | VAS (normalized in 10 points, SD) | Johnson % (completely satisfied + minor reservation) | AOFAS | MOxFQ | Others                                                                 | Post Procedural Surgery Pt (%) | Adverse Events | conclusions                                           |
|-------------------------|-------------------|-----------------------------|---------------------------------------------------|-----------------------|----------------------------------|------------------------------------------------------|-------|-------|------------------------------------------------------------------------|-------------------------------|--------------|----------------------------------------------------------|
| - Thomson C E (9)       | questionnaire     | Corticosteroid injection   | 131 pt 131 feet                                  | 3 months (12 months not blinded) 5 lost (4%) | 3 months post 4.4 (2.3) 12 month unblinded 4.1 (2.9) | 3 months post 4.4 (2.3)                              |       |       | Foot health termometer 64.7 MFPS 35.5, 30.5, 18.9                 |                               | Hypopigmentation 5% | Atrophy of plantar fat pad 3% Symptomatic benefit for at least three months |
| - Markovic M (10)       | questionnaire     | Corticosteroid injection   | 35 pt, 39 feet                                   | 9 months, 0 lost        | 38%+46%                          | FDA pre:43%+46% difficulty Post:51% no difficulty 33% little difficulty |       |       | 12 (31%)                                                      |                               | No complications | Can offer short pain relief, no correlation size pain relief |
| - Park YH (11)          | Clinical reviewed | Corticosteroid injection   | 201 pt                                           | 6 months               | Pre 8.5 (5 to 10), post 2.8 (0 to 10) | 20%+51%                                               |       |       | 40 (19.9%)                                                     |                               | Larger neuromas were associated with failure |
| - Saygi B (12)          | Clinical examination | Corticosteroid injection | 34 pt 12 months, NR                             |                       | 82% complete or partial relief of pain | NR                                                   |       |       | Corticosteroids may have a therapeutic effect                  |                               |              |                                                        |
| - Ruiz Santiago F (13)  | Scheduled consultation | Corticosteroid injection | 62 pt 6 months, 6 lost (9%)                      |                       | Pre 8.5 (0.2) Post 3.4 (0.5) guided, 5.1 (0.7) blinded | MFPDS Pre 44.5 (1.4), post 33.6 (2.3) guided, 37.6 (2.7) blind Satisfied patients 69% guided, 44.4% blinded |       |       | Hypopigmentation 10% Atrophy of plantar fat pad 5% Ultrasound guided provides a statistically significant improvement at same stage of follow-up compared with blinded injections |
| - Lizano-Díez X (14)    | Clinical examination | Corticosteroid injection   | 16 pt 6 months                                   |                       | 37.5%+25%                          | Pre 78.6 (8.2), post 84.5 (13.8)                      |       |       | 7 (44%) Skin atrophy 18.7%                                       |                               | Injection of corticosteroid was not superior to local anesthetic alone |
| - Hau MYT (15)          | Postop questionnaire, telephone interviews | Corticosteroid injection | 36 pt, 45 feet                                   | 4.8 years (0.9) 3 lost (6%) | NR                               | NR                                                   |       |       | 36% asymptomatic                                                 | 6 (15%)                        | NR           | Corticosteroid injection remain effective in over a third of case for 5 years |

1 If mean, SD is given.
### Table 2. Clinical Features of All Included Studies (NR = Not Reported/ Not Clear, SD = Standard Deviation) (Continued)

| Author          | Assessment Method                  | Intervention          | Number of Patients - Number of Feet (if different) | Duration of Follow-up Lost in Follow-up | VAS (normalized in 10 points) (SD) | Johnson % (Completedly Satisfied + Minor Reservation) | AOFAS | MOxFQ | Others | Post Procedural Surgery Pt (%) | Adverse Events | Conclusions                                                                 |
|-----------------|------------------------------------|-----------------------|--------------------------------------------------|-----------------------------------------|-----------------------------------|--------------------------------------------------------|--------|-------|--------|-------------------------------|----------------|------------------------------------------------------------------------------|
| Maki D (16)     | Clinical examination               | Corticosteroid injection | 39 pt 12 months                                 | Pre 6.6 (1.3) Post 6                   | 15.3% + 7.7%                      | Pre 73.5 (13.5), post 75.2 (NR)                       | 0      |       |        |                               | 0              | No skin related complications Corticosteroid injection resulted in short term pain relief, more effectiveness for smaller lesions |
| Mahadevan D (17)| Clinical examination               | Corticosteroid injection | 40 pt, 50 feet 12 months Lost 4 pt, 5 feet (10%) | Pre 7.0 (2.4) Post 3.3                 | 17.7% + 24.5%                    | Pre 56.5 (41.8 to 80), post 19 (9 to 76)             | 14 (61%)|       |        |                               | 18 (31.5%)      | Local depigmentation 2.2% Larger neuromas and younger patients predicted the need for further intervention |
| Mahadevan D (18)| Data extraction and contacted patients | Corticosteroid injection | 54 pt, 57 feet 2 years, 1 lost (2%)              | Pre 8.6 (1.2), post 2.9 (3.1)          |                                | Post 85.1 (13.4)                                   |        |       |        |                               | 12 (9.6%)       | Transitory forefoot swelling                                                  |
| Samaila EM (19) | Clinical assessment                | Phenol injection       | 115 pt, 125 feet 8.3 years                       | Pre 8.6 (1.2), post 2.9 (3.1)          |                                | Post 85.1 (13.4)                                   |        |       |        |                               | 74.5% satisfied 140 feet (25.9%) no resolution | 50 (9.3%) Local inflammatory reaction |
| Pasquali C (20) | NR                                 | Alcohol injection      | 508 pt, 540 feet 1 year                          | Pre 8.7 (6 to 10) Post 3.6 (0 to 9)    |                                | Post 85.1 (13.4)                                   |        |       |        |                               | 74.5% satisfied 140 feet (25.9%) no resolution | 50 (9.3%) Local inflammatory reaction |
| Perini L (21)   | interview                          | Alcohol injection      | 220 pt 19 months (15 to 24)                       |                                |                                | Post 85.1 (13.4)                                   |        |       |        |                               | 74.5% satisfied 140 feet (25.9%) no resolution | 50 (9.3%) Local inflammatory reaction |
| Pabinger C (22) | Clinical assessment                | Alcohol injection      | 30 pt, 33 feet 5 years                            | Pre 7.8 (0.8), post 0.7 (0.8)          |                                | Post 85.1 (13.4)                                   |        |       |        |                               | 74.5% satisfied 140 feet (25.9%) no resolution | 50 (9.3%) Local inflammatory reaction |
| Hughes RJ (23)  | Questionnaire and follow up by phone | Alcohol injection      | 101 pt 10.5 months 1 lost (1%)                    | Pre 8 (6 to 1 0), post 0-1 (0 to 10)   |                                | Post 85.1 (13.4)                                   |        |       |        |                               | 74.5% satisfied 140 feet (25.9%) no resolution | 50 (9.3%) Local inflammatory reaction |
| Gurdezzi S (24) | NR                                 | Alcohol injection      | 60 pt 5 years                                    | Pre 8 (NR) Post 4 (NR)                 | 33% + 22%                         | Post 85.1 (13.4)                                   |        |       |        |                               | 74.5% satisfied 140 feet (25.9%) no resolution | 50 (9.3%) Local inflammatory reaction |
| Assessment method | Intervention | Number of Patients | Duration of Follow-up (months) | Number of Feet (if different) | Adverse Events | Post Procedural Surgery (Pt (%)) | VAS (normalized in 10 points) (SD) | MOxFQ | AOIFAS | Post | Procedural Surgery Post | Other | Conclusions |
|-------------------|--------------|---------------------|-------------------------------|-----------------------------|----------------|-----------------------------|---------------------------------|-------|---------|----------------|--------------------|--------|-------------|------------------|
| Clinical examination | Alcohol injection | 92 pt, 104 feet | 2 years (1 to 3.3) | 0 lost | 36(89%) total or partial sensory relief | Post 88 (100 to 51) | 14.3 (NR) | 40pt, 40 feet | 10 months | Pre 8.5 (4 to 10), post 4.2 (0 to 10) | 17 (20%) | Greater procedural success in patient under 55 years, or in solitary neuromas | 1 pt (1%) allergic reaction, 1 pt (1%) periprosthetic pain |
| Telephone followup | Alcohol injection | 75 pt, 87 feet | 14.3 (NR) | 17 pt not considered | Partial or total symptomatic relief, 66% complete response, 33% complete resolution | Post 17 (0 to 24) | 11 months | 42pt, 49 feet | 1 month | Pre 8.5, post 4 (2 to 10) | 30 (35%) no improvement in pain from baseline | 30 (60%) no improvement in symptoms or resolved (16 pt, 33%) | 12 (24%) |
| Telephone followup | Capsaicin injection | 30 feet | 30 feet | 1 month | Mean reduction of pain from baseline Pre 5.9, post 2.3 | Post 92.5 (medium improvement score) | 92 (60%) | NR | 0 lost (5%) | Pre 2.2 (NR), post 6.5 (NR) | 88% satisfied or very satisfied | No improvement of sensory loss | 89% satisfied |
| Post | Capaicin injection | 30 feet | 30 feet | 1 month | Mean reduction of pain from baseline Pre 5.9, post 2.3 | Post 92.5 (medium improvement score) | 92 (60%) | NR | 0 lost (5%) | Pre 2.2 (NR), post 6.5 (NR) | 88% satisfied or very satisfied | No improvement of sensory loss | 89% satisfied |
| Clinic visit | Alcohol injection | 92 pt, 104 feet | 2 years (1 to 3.3) | 0 lost | 36(89%) total or partial sensory relief | Post 88 (100 to 51) | 14.3 (NR) | 40pt, 40 feet | 10 months | Pre 8.5 (4 to 10), post 4.2 (0 to 10) | 17 (20%) | Greater procedural success in patient under 55 years, or in solitary neuromas | 1 pt (1%) allergic reaction, 1 pt (1%) periprosthetic pain |
| Clinic visit | Capsaicin injection | 30 feet | 30 feet | 1 month | Mean reduction of pain from baseline Pre 5.9, post 2.3 | Post 92.5 (medium improvement score) | 92 (60%) | NR | 0 lost (5%) | Pre 2.2 (NR), post 6.5 (NR) | 88% satisfied or very satisfied | No improvement of sensory loss | 89% satisfied |
| - Lorenzon P (25) | - Lorenzon P (25) | - Lorenzon P (25) | - Lorenzon P (25) | - Lorenzon P (25) | - Lorenzon P (25) | - Lorenzon P (25) | - Lorenzon P (25) | - Lorenzon P (25) | - Lorenzon P (25) | - Lorenzon P (25) | - Lorenzon P (25) | - Lorenzon P (25) | - Lorenzon P (25) | - Lorenzon P (25) |
| - Fanucci E (26) | - Fanucci E (26) | - Fanucci E (26) | - Fanucci E (26) | - Fanucci E (26) | - Fanucci E (26) | - Fanucci E (26) | - Fanucci E (26) | - Fanucci E (26) | - Fanucci E (26) | - Fanucci E (26) | - Fanucci E (26) | - Fanucci E (26) | - Fanucci E (26) | - Fanucci E (26) |
| - Musson RE (27) | - Musson RE (27) | - Musson RE (27) | - Musson RE (27) | - Musson RE (27) | - Musson RE (27) | - Musson RE (27) | - Musson RE (27) | - Musson RE (27) | - Musson RE (27) | - Musson RE (27) | - Musson RE (27) | - Musson RE (27) | - Musson RE (27) | - Musson RE (27) |
| - Mason JD (28) | - Mason JD (28) | - Mason JD (28) | - Mason JD (28) | - Mason JD (28) | - Mason JD (28) | - Mason JD (28) | - Mason JD (28) | - Mason JD (28) | - Mason JD (28) | - Mason JD (28) | - Mason JD (28) | - Mason JD (28) | - Mason JD (28) | - Mason JD (28) |
| - Campbell CM (29) | - Campbell CM (29) | - Campbell CM (29) | - Campbell CM (29) | - Campbell CM (29) | - Campbell CM (29) | - Campbell CM (29) | - Campbell CM (29) | - Campbell CM (29) | - Campbell CM (29) | - Campbell CM (29) | - Campbell CM (29) | - Campbell CM (29) | - Campbell CM (29) | - Campbell CM (29) |
| - Lee K [30] | - Lee K [30] | - Lee K [30] | - Lee K [30] | - Lee K [30] | - Lee K [30] | - Lee K [30] | - Lee K [30] | - Lee K [30] | - Lee K [30] | - Lee K [30] | - Lee K [30] | - Lee K [30] | - Lee K [30] | - Lee K [30] |
| - Shah R (31) | - Shah R (31) | - Shah R (31) | - Shah R (31) | - Shah R (31) | - Shah R (31) | - Shah R (31) | - Shah R (31) | - Shah R (31) | - Shah R (31) | - Shah R (31) | - Shah R (31) | - Shah R (31) | - Shah R (31) | - Shah R (31) |
| - Connors JC (32) | - Connors JC (32) | - Connors JC (32) | - Connors JC (32) | - Connors JC (32) | - Connors JC (32) | - Connors JC (32) | - Connors JC (32) | - Connors JC (32) | - Connors JC (32) | - Connors JC (32) | - Connors JC (32) | - Connors JC (32) | - Connors JC (32) | - Connors JC (32) |
| - Climent JM (33) | - Climent JM (33) | - Climent JM (33) | - Climent JM (33) | - Climent JM (33) | - Climent JM (33) | - Climent JM (33) | - Climent JM (33) | - Climent JM (33) | - Climent JM (33) | - Climent JM (33) | - Climent JM (33) | - Climent JM (33) | - Climent JM (33) | - Climent JM (33) | - Climent JM (33) |

Symptom recurrence is often associated with mechanical metatarsalgia.
Data analysis

This is a systematic review, not a meta-analysis. We presented the outcome of each research as a relative number, then we performed proportions to convert results in percentage.

We performed the bias assessment process as described in Cochrane Handbook and the quality of studies as exposed in NOS (34,35).

The findings are not integrated with statistical analysis, even though we took those findings into account as far as quality is concerned.

Results

A total of 1086 records were yielded through the initial literature search. After the first screening (removing of duplicates and not pertinent studies), we examined 36 full texts. Among these, 25 studies have been selected for the review. The remaining 11 were excluded for different reasons: 1 study was written in a language other than English, 8 studies had irrelevant content, 1 was a duplicate paper, and another one did not meet other inclusion criteria, because the type of metatarsalgia is not clearly illustrated, and it lacked outcome in terms of patients’ satisfaction.

The abovementioned studies have been submitted to a quality assessment, as reported in tables 1 and 2. The randomization procedure was used only in 7 studies, of which 6 about corticosteroid injections and 1 about capsaicin injection; in these studies, the method is not always clearly described.

Among the studies about alcohol injection, no one has been randomized; many are retrospective case series.

In general, several studies suffer a patient loss in follow up; in 2 of them, the loss is more than 25%. In 2 other studies, patients initially treated are successively excluded without any explanation about the reason why this happens.

Only in 5 studies the outcome results are blinded.

Included studies description

The data of included studies was summarized in table 1 and 2. There was a total amount of 25 studies (9 to 32), all about Morton’s neuroma injections, but with a high variability of the injected substance: 10 studies dealt with corticosteroids (9 to 18), 9 with alcohol (20 to 28), 1 with phenol (19), 1 with capsaicin (29), 1 with botulinum (33), 1 with hyaluronic acid (30), 2 with use of radiofrequency ablation (31-32).

A total of 2243 Morton’s neuroma cases were included.

In this cohort mean age was 53.4 years, and the proportion females/males was 78.5/21.5. There was no significant difference regarding age or gender in the six groups already mentioned.

In terms of type of injection for the 2243 cases, there were: 674 treated with corticosteroids, 1234 with alcohol, 124 with phenol, 30 with capsaicin, 17 with botulinum, 83 with of hyaluronic acid, 80 with radiofrequency ablation.

There were only 6 blinded randomized trial, in the 25 selected studies (9-6-7-8-11-29).

The majority of the studies were neither randomized nor blinded; many of them were case series, prospective or retrospective, to be considered at risk of bias. In the same way, some other studies are characterized by a high loss of participants on follow-up, or not clear cohort formation.

Pain and satisfaction outcome

A high heterogeneity of outcome measures is in use, so that a comparison is difficult. The length of follow up affects the evaluation process as well, since we know that recurrence of Morton’s neuroma is a possible event. A too early end of the follow up may lead to overoptimistic results.

Corticosteroid injection

There are 10 studies which analyze corticosteroid injections (9 to 18).

The incidence for complete or partial pain relief, taken into consideration in 3 studies, was estimated to be 58%.

Pain assessment score, VAS (Visual Analogic Scale), considered in a total of 6 studies, decreased from 7 (Standard Deviation 1.5) in the pretreatment to 4.4 (SD 1.1) in the post treatment control.
Johnson score, which defines satisfaction in four levels: complete, with minor or major reservations or not existing - registered a mean of 25.7% patient completely satisfied, and 21% of satisfied with minor reservations in the 5 studies in which it was in use.

The need of surgical treatment was found to be 28.9%.

The length of follow up was of 12.6 (SD 16.3) months, with 6 studies of 12 months or more, and 2 studies of 24 months or more.

**Alcohol injection**

9 studies analyze alcohol injections (20 to 28). The incidence for complete or partial pain relief, taken into consideration in 7 studies, was estimated to be 71%.

VAS, considered in a total of 6 studies, decreased from 8.1 (SD 0.3) in the pretreatment to 2.4 (SD 2.1) in the post treatment control.

Johnson score registered a mean of 51% patient completely satisfied, and 22.6% of satisfied with minor reservations in the 3 studies in which it was in use.

The need of surgical treatment was found to be 14.8%.

The length of follow up was of 17.8 (SD 20.5) months, with 6 studies of 12 months or more, and 3 studies of 24 months or more.

Others injections: phenol, capsaicin, botulinum toxin A, hyaluronic acid, and use of radiofrequency ablation.

Only one retrospective case series is about Phenol injections (19); the complete or partial pain relief was estimated to be 71.2%. VAS decreased from 8.584 in the pretreatment to 2.885 in the post treatment control. Johnson score was not considered.

The need for surgical treatment was tested to be 9.6%.

The length of follow up was of 99.6 months.

Capsaicin injection was investigated in one randomized blinded trial (29): VAS decreased from 5.9 in the pretreatment to 2.3 in the post treatment control.

The length of follow up was only of 1 month.

Botulinum toxin A injection was investigated in one study as well (33): the incidence of complete or partial pain relief was estimated to be 70.6%. VAS decreased from 7 in the pretreatment to 3.7 in the post treatment control.

The length of follow up was only of 3 months.

A retrospective study regards hyaluronic acid injection (30): the incidence of complete or partial pain relief was estimated to be 84%.

VAS decreased from 7.3 in the pretreatment to 2.3 in the post treatment control.

The length of follow up was of 12 months.

Finally, two items report the experience with radiofrequency ablation (31-32): they registered a mean of 89% patient completely satisfied, VAS decreased from 7 in the pretreatment to 1 in the post treatment control.

The length of follow up was of 23.9 months.

Many others outcome scores are in use (AOFAS, MOxFQ, Foot Health Thermometer, MFPDS, FDA) according to the considered studies. Because of the changeable presence in the items, they are reported only in table 2.

**Discussion**

This study overviews the current available literature for the different infiltration treatments of Morton’s Neuroma in terms of pain relief and patient satisfaction. The main drawback relies on the difficulty of comparing the results due to the so many outcome measures and different follow up periods. It is well known that after a treatment of Morton’s neuroma (also surgical treatment) pain can re-present after a period of wellness that can last for more than two years. For these reasons, follow ups of 24 months or more are more relevant in terms of the evaluation of persistent results. We discovered a low quality of the studies available in this common condition. There is weak evidence, due to heterogeneity of the trials, lack of details pertaining randomization and loss to follow-up. Furthermore, the randomization trials are very few.

The majority of the studies regards corticosteroids or alcohol injections. In term of results, in corticosteroid injections partial or total pain relief was estimated to be 52%, with a mean follow up of 12.6 months, but in 40% of the studies the follow up was less than one year. Many authors conclude that corticosteroid injection provide a benefit which is only temporary (9-10-14-16).
The two studies characterized by a longer follow up - Hau: 4.8 years (15); Mahadevan: 3 years (17) - conclude that corticosteroid injections remain effective respectively in over a third (36%) and in about one half (49%) of the patients. In general, corticosteroid injection procedure is characterized by a very low percentage of complications (local hypopigmentation, atrophy of plantar fat pad, skin atrophy). Anyway, as a matter of fact, a certain percentage of patients remains asymptomatic in the long run. These favorable results may be related to neuromas of recent onset, because in these cases the neural fibrosis is not structured yet (11-18).

Better results are shown after alcohol injection (20 to 28), with a complete or partial pain relief of 71% and with a mean follow up of 17.8 months.

Pabinger (22), in a 5-years follow up, observes 82% of success rate, Perini (21) in a 19 months follow up finds a 72% of responders, Lorenzon (25), in a two years follow up observes a 88% of patients satisfied or satisfied with minor reservations.

Gurdezi (24) reported unfavorable results after a 5-years follow up of alcohol injections. This author considers 60 patients previously observed in a former study of 101 patients by Hughes (23). It is not specified the method chosen to select those 60 patients in the previous cohort of 101. Moreover, of the 60 patients selected, only 45 were actually available for the follow up. Gurdezi concludes that only 29% remained symptoms free and 35% had undergone surgical treatment. This article, that is often quoted in reviews and papers regarding Morton’s Neuroma, has the merit to raise the question of recurrence after alcohol injection, but according to us it presents a high risk of bias.

In general, there is a high heterogeneity regarding the percentage of alcohol employed, that varies from 4% to 70%. A lower percentage of alcohol concentration in the older studies resulted in a higher mean number of session and in a higher number of relapses. Gurdezi uses a 20% solution, which is a concentration currently deemed not suitable for structural changes of the nerve.

Therefore, alcohol injection seems to provide long term clinical benefits in a considerable number of patients. In the post injection period, few adverse events are seen, but we have to consider a period of exacerbation of local pain due to inflammation related to the use of alcohol.

The use of Phenol points out good results in the long run as well (19). The feared adverse event of skin necrosis is not reported in the cohort in exam. Unfortunately, this is an isolated experience, since no other items have been produced in English on this specific subject.

Botulinum and capsaicin were experimented with a very short follow up (3 months and 1 month). Because of the action mechanism, we do not expect to see long-term benefits (33-29).

The study with hyaluronic acid (30), injected around (and not in) the nerve is very promising, with a 84% of partial or complete pain relief after one year. The positive effects could be attributed to the anti-inflammatory activity enhancing cell proliferation and collagen deposition, and reducing scar formation of peripheral nerves. To understand if these effects are permanent, other studies and longer follow up will be needed.

Finally, radiofrequency ablation (31-32) seems to offer a convincing minimally invasive alternative. Yet it would be necessary to consider a longer follow up, and the intrinsic cost of instrumentation.

Because of the heterogeneity of the literature, a systematic pooling of data was not possible, nevertheless we are allowed to conclude that corticosteroid and alcohol injection are indicated as first level treatment of Morton’s neuroma.

Surgical treatment of Morton’s neuroma offers a higher possibility of success, but we have to consider that rates of complete pain relief after neurectomy are higher than those of complete satisfaction of the patient, suggesting that some patients do not tolerate the after-effects of surgery (36).

Moreover, adverse events following surgery are common.

Implication for practice

Therapeutic algorithms available in literature recommend starting with conservative and infiltrative treatment, considering surgery only in a second stage; this happens because of the low complication rate of injections, and it is also related to the quality of healing.

Between the infiltrative treatments of Morton’s neuroma, alcohol injections seem to have the best long-term
results, corticosteroid injections are more effective in case of recent onset, and small neuromas in which the inflammatory process and fibrosis are at their onset.

If injections fail, some authors repeat the infiltrative treatment, but surgery has to be considered.

**Implication for research**

Well-designed trials are needed.

Shared follow up outcome measures are necessary.

The follow up has to be at least of two years, for the possibility of relapse.

Morton’s neuroma is frequently associated with mechanical metatarsalgia, and symptoms related with these two conditions are hardly identifiable by the patients; so, the evaluations of outcome should be clinical, not through telephone interview or questionnaire.

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