

R E V I E W

Infiltrative Therapy of Morton's Neuroma: a Systematic Review of Different Treatment Options

Paolo Lorenzon¹, Carlo Rettore², Andrea Scalvi¹

¹Orthopedics and Traumatology Unit, Hospital of Cittadella, Padua, Italy; ²Radiology Unit, Hospital of Cittadella, Padua, Italy

Abstract. The aim of this study is to systematically review the literature on clinical outcomes of patients who have undergone infiltrative therapy for treatment of Morton's neuroma. As many kinds of substances are injected, the main outcome defines which treatment provides the best results in term of patient's satisfaction and pain relief, so that it would be possible to choose the best option. Many electronic databases were searched on July 2021; we have included prospective and retrospective case series, and randomized controlled trials of infiltrative treatments in patients with primary diagnosis of Morton's neuroma. The search returned 25 studies which met the inclusion criteria, with a total of 2243 cases. The incidence of outcomes was extracted and analyzed. Although many studies demonstrated favorable results in terms of pain relief and patient's satisfaction employing different substances for infiltration, alcohol injection appears results on long run. (www.actabiomedica.it)

Keywords: Morton's neuroma injection, Morton's neuroma treatment, Morton's neuroma review, Morton's neuroma alcohol, Morton's neuroma corticosteroid, Morton's neuroma hyaluronic acid, Morton's neuroma conservative treatment

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 term 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 systemic 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.

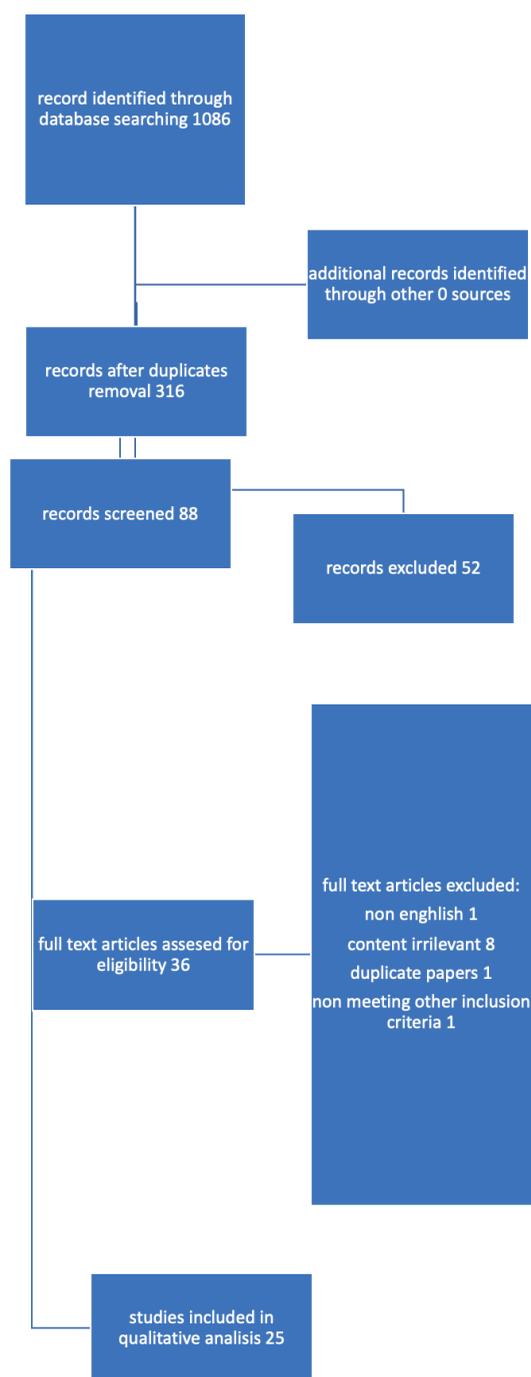


Figure 1. Flow chart: procedure for paper selection

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 Ultrasound guided	Patient blinded randomized trial	85% f, 15% m	53 years
- Markovic M (10)	2008	Sydney, Australia	2002–2003	Corticosteroid injection Ultrasound guided	Prospective case series	80% f, 20% m	54 years
- Park YH (11)	2017	Seoul-Ansan, Korea	2010–2016	Corticosteroid injection Ultrasound guided	Retrospective case series	76% f, 24% m	56.3 years
- Saygi B (12)	2005	Istanbul, Turkey	NR	Corticosteroid injection Not ultrasound guided	Randomized	87% f, 13% m	51.9 years
- Ruiz Santiago F (13)	2019	Granada, Spain	NR	Corticosteroid injection Ultrasound guided vs not guided	Evaluator-blinded randomized trial	89% f, 11% m	52.2 years
- Lizano-Díez X (14)	2017	Barcelona, Spain	2013–2015	Corticosteroid injection Not ultrasound guided	Prospective, double blinded, randomized, placebo controlled	75% f, 25% m	57.7 years
- Hau MYT (15)	2021	Leicester-Reading, UK	2012–2014	Corticosteroid injection Ultrasound guided vs not guided	Prospective randomized	68% f, 32% m	62.6
- Makki D (16)	2012	Leytonstone-London, UK	NR	Corticosteroid injection Ultrasound guided	Prospective comparative	62% f, 38% m	31.7 years
- Mahadevan D (17)	2016	Leicester, UK	2012–2014	Corticosteroid injection Ultrasound guided vs not guided	Double blind randomized controlled	73% f, 27% m	57.8 years
- Mahadevan D (18)	2015	Leicester, UK	2009–2012	Corticosteroid injection Ultrasound guided	Retrospective case series	79% f, 21% m	55.4 years
- Samaila (19)	2020	Verona, Italy	2000–2016	Phenol injection Electrostimulation guidance	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 Ultrasound guided	Retrospective case series	91.3% f, 8.7% m	57 years
- Perini L (21)	2016	Abano-Verona, Italy	2010–2011	Alcohol (50%) injection Ultrasound guided	Retrospective case series	85% f, 15% m	55.8 years
- Pabinger C (22)	2020	Innsbruck-Graz, Austria	2012	Alcohol (70%) injection Electrostimulation guidance	Prospective case series	73% f, 23% m	53 years

(Continued)

Table 1. design and demographic characteristics of all included studies (NR = not reported/ not clear) (*Continued*)

Author	Year	Location	Study Period	Intervention	Study Type	Gender	Mean Age
- Hughes RJ (23)	2007	Middlesex, UK	2004–2005	Alcohol (20%) injection Ultrasound guided	Prospective case series	83% f, 17% m	53.8 years
- Gurdezi S (24)	2013	Kingstone upon Thames, UK	2004–2007	Alcohol (20%) injection Ultrasound guided	Prospective case series	87% f, 13% m	53.5 years
- Lorenzon P (25)	2018	Cittadella, Italy	2012–2014	Alcohol (30%) injection Ultrasound guided	Retrospective case series	85% f, 15% m	56.5 years
- Fanucci E (26)	2004	Rome, Italy	1999–2001	Alcohol (30%) injection Ultrasound guided	Prospective case series	83% f, 17% m	48 years
- Musson RE (27)	2012	Oxford, UK	2008–2008	Alcohol (20%) injection Ultrasound guided	Retrospective case series	88% f, 12% m	57.5 years
- Mozena JD (28)	2007	Portland, USA	2003–2004	Alcohol (4%) injection	Retrospective case series	62% f, 38% m	49.8 years
- Campbell CM (29)	2016	Baltimore, USA	NR	Capsaicin injection not ultrasound guided	Randomized double blind placebo controlled	83% f, 17% m	52.8 years
- Lee K (30)	2018	Gyunggi- Seoul- Gangwon, Korea	NR	Hyaluronic acid perineural injection Ultrasound guided	Retrospective case series	90% f, 10% m	48 years
- Shah R (31)	2019	Birmingham, UK	NR	Radiofrequency Ultrasound guided	Prospective case series	78% f, 22% m	57 years
- Connors JC (32)	2020	Independence- Denver, USA	2010–2012	Radiofrequency Electrostimulation guidance	Prospective case series	78% f, 22% m	Not specified
- Climent JM (33)	2013	Alicante - Yecla – Torrevieja, Spain	NR	botulinum toxin A injection	Prospective case series	41.2% f, 58.8% m	58.2 years

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 ¹ Lost in Follow-up	VAS (normalized in 10 points) (SD)	Johnson % (completely satisfied+ minor reseration)	AOFAS	MOxFO	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)				Foot health termometer 64.7 MFPDS 35.5, 30.5, 18.9		Hypopigmentation 5% Atrophy of plantar fat pad 3%	Symptomatic benefit for at least three months
- Markkovic 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	37.5%+25%			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	Pre 4.8 (0.2), post 2.8 (0.3)		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		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 % (completely satisfied+ minor reservation)	AOEAS	MOxFAQ	Others	Post Procedural Surgery Pt (%)	Adverse Events	Conclusions
- Makki 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	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%)	Local depigmentation 2.2%	
- Mahadevan D (18)	Data extraction and contacted patients	Corticosteroid injection	54 pt, 57 feet	2 years, 1 lost (2%)						18 (31.5%)	NR	Larger neuromas and younger patients predicted the need for further intervention
- Samaila EM (19)	Clinical assessment	Phenol injection	115 pt, 125 feet	8.3 years (4.6)	Pre 8.6 (1.2), post 2.9 (3.1)		Post 85.1 (13.4)			12 (9.6%)	Transitory forefoot swelling	
- Pasquali C (20)	NR	Alcohol injection	508 pt, 540 feet	1 year	Pre 8.7 (6 to 10) Post 3.6 (0 to 9)				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)					72% responder	14 (22.9%)	3 pt (1.2%) relapsed, Worsening of symptoms 0.9%, hypo/anesthesia in 80.0%	
- Pabinger C (22)	Clinical assessment	Alcohol injection	30 pt, 33 feet	5 years (2.6 to 7.6) 0 lost	Pre 7.8 (0.8), post 0.7 (0.8)		Pre 72 (4.5), post 93 (1)		82% success rate	0	79% temporary numbness, 70% mild swelling	Higher percentage (70%) of alcohol is safe
- Hughes RJ (23)	Questionnaire and follow up by phone	Alcohol injection	101 pt	10.5 months 1 lost (1%)	Pre 8 (6 to 10), post 0-1 (0 to 10)				94% improvement 84% totally pain free		16.8% transitory increased local pain	
- Gurdezi S (24)	NR	Alcohol injection	60 pt	5 years (2.8-6) 15 lost (25%)	Pre 8 (NR) Post 4 (NR)	33%+22%		13 pz 29% sintoms free		16 (35%) +13 pz, (29%) relapse	9 pt immense pain in side of injection 2 pt ongoing numbness of toes	Alcohol injection does not offer permanent resolution

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 % (completely satisfied+ minor reservation)	AOEAS	MOxFAQ	Others	Post Procedural Surgery Pt (%)	Adverse Events	Conclusions
- Lorenzon P (25)	Clinical examination	Alcohol injection	92 pt, 104 feet	2 years (1 to 3.3) 0 lost	Post 1 (0 to 8)	65%+23%	Post 88 (100 to 51)			3 (2.8%)	6% relapse 25% reduced sensitivity	Symptom recurrence is often associated with mechanical metatarsalgia
- Fanucci E (26)	NR	Alcohol injection	40pt, 40 feet	10 months		52%+22%			36(90%) total or partial symptomatic relief	4 (10%)	6 pt (15%) transitory plantar pain	
- Musson RE (27)	Telephone followup	Alcohol injection	75 pt, 87 feet, 17 pt not considered	14.3 (NR) months	Pre 8.5 (4 to10), post 4.2 (0 to10)				Partial or total response 66%, 33% complete resolution 30 (35%) no improvement	17 (20%)	1 pt (1%)allergic reaction, 1 pt (1%) periprocedural pain	Greater procedural success in patient under 55 years, or in solitary neuromas
- Mozena JD (28)	NR	Alcohol injection	42 pt, 49 feet	11 (2 to 24) months					30 (60%) symptoms improved or resolved (16 pz, 33%)	12 (24%)	3(6%) mild complications	
- Campbell CM (29)	Clinic visit	Capsaicin injection	30 feet	1 month				Mean reduction of pain from baseline Pre 5.9, post 2.3			Mild erythema, edema, hemorrhage	
- Lee K (30)	NR	Hyaluronic acid injection	83 pt	12 months	Pre 7.3 (NR), post 2.3 (NR)		Pre 32.2 (NR), post 86.5 (NR)		84% satisfied or very satisfied		3(3.6%) severe pain for 1-2 days, 2(2.4%) discomfort	No improvement of sensory loss
- Shah R (31)	telephonic	Radiofrequency ablation	18 pt, 22 feet	8 months, 1 lost (5%)	Pre 8 (7 to 9), post 1 (1 to 4)				89% satisfied	NR	1 pt (4%)new twitching of second toe	Excellent initial results, need further studies on long term outcomes
- Connors JC (32)	Post questionnaire or visit	Radiofrequency ablation	32 pt (from a cohort of 58 pt)	2.5 (2 to 4) years, 16 lost (27%)	Pre 6 (4 to 8), post1 (0 to 5)			Post 92.5 (medium improvement score)			NR	NR
- Climent JM (33)		Botulinum toxin a injection	17 pt	3 months	Pre 7 (1.4), post 3.7 (3.5)				12 (70.6%) improvement 5(29.4%) no change FHSQ pre 38.88, post 57		NR	NR

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 duplications 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 level - 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 sessions 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.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Correspondence:

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Paolo Lorenzon,

Ospedale Civile di Cittadella (Padova, Italy),

U. O. di Ortopedia e Traumatologia,

via Casa di Ricovero 40, 35013 Cittadella (PD)

Phone: +39 049 9424671;

FAX +39 049 9424681

E-mail: Paolo.lorenzoni@aulss6.veneto.it