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Sclerosing alcohol injections for the management of intermetatarsal neuromas: a systematic review

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Highlights

► This review found insufficient high-quality research evidence to afford conclusions on the management of intermetatarsal neuroma with alcohol sclerosing agent injections.

► Alcohol injections appear to be safe although a short-term side effect of a flogistic reaction may occur.

► Given the overall lack of high level evidence to support the effective management of intermetatarsal neuroma, a staged management approach may be a logical treatment option, until further research evidence to support the respective treatment becomes available. Alcohol injections could be included in this stepwise approach when other more evidence-based treatment fail.

ABSTRACT

An intermetatarsal neuroma is a plantar digital neuritis causing metatarsalgia of the affected inter-metatarsal space. At present the evidence to support the management of the condition is poor with only some quality evidence supporting the short-term management of intermetatarsal neuromas using steroid injections. Some authors have supported the use of alcohol sclerosing intra-lesional injections to treat intermetatarsal neuromas. Following a search of the evidence 11 articles were identified. The systematic review found that alcohol injections appear to be safe although some papers report a short-term side effect of a flogistic reaction and there are variances in the alcohol concentration used and guiding verses not guiding the injection using ultrasound imaging. Some of the evidence may suggest a sclerosing histological effect of the nerve. However, all the studies reviewed present a research design offering a low level of evidence that is open to methodological biases and interpretation. Thus, this review found insufficient high-quality research evidence to afford conclusions on the management of intermetatarsal neuromas with alcohol sclerosing agent injections.

Abbreviations: VAS , Visual Analogue Scale; QoL: Quality of life; RCT: Randomised controlled trial

Keywords: Systematic review; intermetatarsal neuroma; Morton's neuroma; alcohol injections

1 Introduction

Plantar interdigital neuroma was first described by Civinini in 1835 and later by Durlacher in 1845.[1] In 1876 Morton presented 12 case studies of neuralgic pain affecting the fourth intermetatarsal space. The same paper also commented on a further 3 cases (although not in any depth).[2] Although most papers refer to Morton's neuroma when describing any neuroma in the forefoot, a more precise description would be intermetartarsal neuroma since Morton only referred to the $3^{rd}/4^{th}$ intermetartarsal space. Thus, the condition now commonly known as Morton's neuroma or intermetatarsal neuroma is described as an entrapment or degenerative neuropathy secondary to mechanically induced compression of the intermetatarsal/interdigital nerve as it traverses under the transverse intermetatarsal ligament.[3-7]

Intermetatarsal neuromas are diagnosed clinically following manual tests that reproduce the symptoms [1,8-10] and confirmed by advanced diagnostic investigations which may include ultrasound imaging[11-15] or Magnetic Resonance Imaging techniques.[16-21] Advanced diagnostic investigations have suggested that intermetatarsal neuromas become symptomatic when the transverse diameter is 5mm or more.[13,19-21]

The is a lack of current evidence to support effective management of intermetatarsal neuromas although steroid injection appears to be supported by higher level evidence with a number of randomised control studies although long-term evidence is lacking.[22]

2 Background

3 Definition

Intermetatarsal neuromas are described as a common neuralgic pain affecting the forefoot. The inter-metatarsal space between the $3^{rd}/4^{th}$ is most typically affected followed by inter-metatarsal spaces $2^{nd}/3^{rd}$, $1^{st}/2^{nd}$ and $4^{th}/5^{th}$.[22-29]

Epidemiology

Both feet appear to be equally affected however it is uncommon to find cases of bilateral presentation.[22] Similarly, it is not typical to find more than one neuroma affecting the same foot.[22] With regards to gender the condition appears to be 8-10 times more prevalent in females than males with a mean age distribution of 45-50 years.[30-32] The third web space is most commonly affected with the first and fourth rarely affected.[32]

Symptoms

Patients usually present complaining of a sharp, neuralgic, lancing pain, severe in onset that occurs suddenly when walking, especially with certain shoes which usually have a narrow toe-box. Some patients report that they have to stop walking, take their shoe off and massage or manipulate the toes to achieve some relief of symptoms. Other reported symptoms are described as tingling or burning sensation.[32] In the

worst cases, patients often report significant pain that can be debilitating and affect the person's quality of life with regards to limitations in ambulation.[3]

Diagnosis

Diagnosis is usually based on clinical examination which has been reported to have good clinical specificity, with diagnostic investigations used in cases where clinical diagnosis is not clear and for those progressing for surgical intervention.[33,34] With regards to clinical examination, using more than one clinical test to confirm the diagnosis has proved more effective.[34,35] The most commonly used advanced diagnostic modality for diagnosis of intermetatarsal neuromas is ultrasound imaging which has been shown to be sensitive and reliable.[36]

3.1.1 Animal studies

A study by Rengachary et al (1983) used graded concentrations of alcohol (5, 10, 25, and 50%) that was injected extra and intra-neurally using 56 rats sacrificed at 25 days. No control group was used. The degree of nerve destruction was graded in the range of 1 to 4 depending on the percentage of axons in the studies specimen showing pathological changes (Grade 1: 25% of axons showed pathological damage; Grade 2: 50% of axons showed pathological damage; Grade 3: 75% of axons showed pathological damage; and Grade 4: 100% of axons showed pathological damage). All extra-neural injections showed no histological neural changes, however, intra-neural injections showed noticeable destruction and this was dependant on concentration used. At five to ten percent of alcohol concentration no intra-neural damage was observed. At 25% concentration Grade 1 changes was reported and at 50% concentration Grade 2 changes were seen.[37] Another study by Mazoch et al (2014) also used the sciatic nerve in 22 rats as a model to evaluate the effects of alcohol injections in nerve tissue as a potential model for treatment of intermetatarsal neuromas.[38] Different concentrations of alcohol injections (that is, 4%, 20% and 30%) with 0.5% Marcaine was used and injected intra-neural, peri-neural and peri-muscular. Mazoch et al (2014) concluded that regardless of the concentration of alcohol or technique used there was no histologic evidence of cell necrosis or inflammation in the nerve tissue. However, all the rats were sacrificed at 10 days post injection, a higher range of concentrations could have been used and no repeated injections were carried out to simulate clinical studies/practice hence, it is possible that not enough time was allowed for the nerve tissue changes to occur or maybe that repeated injections are required to achieve pathological nerve effects.

Management

Symptomatic neuromas cause forefoot neuralgic pain radiating to the affected digits.[9,10] These are initially treated with conservative measures including patient education, pads, orthosis, footwear modifications and steroid injections.[1,8] Bennett et al. (1995) found that 50% (n=57/115) of subjects benefited from footwear modifications, pads and patient education. A Cochrane's review found no evidence to support the use of orthosis.[22]

Cortisone Injection Therapy

Steroid injections are routinely used as an initial or adjunct treatment choice in conjunction with stretching, footwear advice and foot orthosis management. In retrospective studies Bennett (1995) found that 47% of those who received a steroid injection demonstrated an improvement in symptoms and Greenfield (1984) found that most were asymptomatic after two years; however, other retrospective studies have reported poor outcomes with steroid injections.[8,30,39] Rasmussen (1996) conducted a retrospective study involving 43 patients (51 feet) and found that in 47% (n=24 feet) surgery was later required.[39] However, these retrospective studies should be interpreted with caution as they were not RCTs and their internal validity may be questioned.

Thomson et al (2013) carried out a pragmatic, patient blinded RCT within a hospital orthopaedic setting. A total of 131 patients were recruited and randomised into a placebo group (receiving 2mL 1% lignocaine alone) and trial group (receiving 1mL methylprednisolone [40mg] and 1mL 2% lignocaine). A diagnostic ultrasound was used to confirm the presence of a neuroma and all injections were guide by sonography. The clinical outcome measures used was a visual analogue scale (VAS) and quality of life. A clinical and statistical difference was reported by one and three months with improvements in the trial group suggesting that steroid injections are effective by up to three months with the size of the lesion not influencing the treatment effect.[40] However, more long term studies are needed to assess the long term effects of steroid injections. With regards to steroid injections, there may be a risk of ``steroid flare", anaphylaxis, skin atrophy or altered pigmentation with the evidence suggesting that steroid injections are of limited value providing short to medium term relief for patients awaiting surgery.[22,23,40-43]

Summary of Management

In conclusion to the overall management for intermetatarsal neuromas, where conservative measures fail there is no other options available but surgical management, although there is still debate with regards to the best surgical technique, and there are also complications and failure rates associated with these procedures.[22] Thus, despite this staged management approach, the current evidence-base for the effectiveness of conservative and surgical management of intermetatarsal neuromas is still insufficient.[22]

Methods

Justification for Systematic Review

As a consequence, more research evidence is required to support clinical guidelines, not only is more research evidence emerging with regards to the already established clinical treatments for intermetatarsal neuromas but also potential new treatments to manage this condition are being explored. Dockery in 1999 reported the first study using alcohol injections to conservatively manage intermetatarsal neuroma with this method then gaining popularity with numerous publications since then.[9] This review will critically appraise current evidence for the management of intermetatarsal neuromas with alcohol injections.

Review Question

PICO (population, intervention, comparison and outcome) format was used to define the reviews research question as follows: Does alcohol injections [Intervention] provide effective clinical outcomes [Outcome] compared to other treatments [Comparison] for the treatment of intermetatarsal neuromas [Population]?

Search Strategy

An electronic search of the Cochrane's Group Trials register, EBSCO Host Research Databases (MEDLINE and CINAHL Plus) was carried out on 26th June 2017.' EBSCO Host Research Databases (MEDLINE and CINAHL Plus) was searched 1981 to 2017. The PICO search strategy allowed the development of the search strategy and the population and intervention was used with outcome and comparisons left open to increase numbers identified by search strategy. The references of all selected papers were also screened.

MEDLINE and CINAHL Plus Search Strategy

The following search strategy was carried out: 1)Morto*; 2) interdigital OR inter-digital OR plantar; 3) neurom*; 4) neur*; 5) 1 OR 2; 6) 3 OR 4; 7) 5 AND 6; 8) alcohol; 10) 7 AND 8

Cochrane's Neuromuscular Disease Group Trials register

The following search strategy was carried out: Morton OR Morton's AND neuroma OR neuromas. This was used as the number of publications in the Cochranes library are limited and the search was kept as open as possible.

Review methods

Two reviewers (DS and AC) independently screened all titles and abstracts for studies identified by the search. Full text papers of potentially eligible studies were retrieved by DS and these were independently screened by DS and AC. Authorship and results were not masked. Any disagreements between the two authors regarding full-text inclusion were resolved by a third reviewer (GM). However, no disagreements occurred between the two reviewers.

DS extracted data from included studies using a standardised pilot tested form. AC checked all the extracted data. If there were any absent or uncertain information, study authors were contacted. Inconsistencies in data extraction were discussed between DS and AC and, if needed, through arbitration by GM. Risk of bias of each included study was rated independently by DS and AC using the following criteria described in the Cochrane Handbook for Systematic Reviews of Interventions.[44]

1. Sequence generation
2. Allocation of concealment
3. Blinding of participants, personnel and outcome assessor
4. Incomplete outcome data

5. Selective outcome reporting

6. Other sources data

For each criterion 'High' indicates a high risk of bias, 'Low' indicates a low risk of bias and 'unclear' identifies an ambiguous or unclear risk of bias.

Inclusion Criteria

The population was patients with a clear diagnosis of intermetatarsal neuroma or its synonyms either clinically and/or using diagnostic imaging. The intervention was any concentration of alcohol injection either guided or non-guided. The comparator was any current reported treatment for intermetatarsal neuroma. The outcome was the Visual Analogue Scale (VAS) and/or any other quality of life or satisfaction tool. Finally, the study designs were randomised control studies (RCT), cohort and case-series/case-control studies. Studies other than RCTs were included as previous Cochranes reviews have not identified any RCTs using alcohol injections.

Exclusion Criteria

Articles or abstracts not written in English.

Results from search strategy

Following the electronic searches 46 papers were identified, with the Cochrane's Group Trials register proving 1 systematic review and EBSCO Host Research Databases (MEDLINE and CINAHL Plus) 45 articles. No duplicates were identified by the search engines. The titles and abstracts were read by both reviewers independently and following consultation 34 papers were eliminated leaving the remaining 12 articles. One of the articles with an abstract in English was written in Italian, both reviewers agreed that this was a key article, and should be translated and included despite the set exclusion criteria.[45] The full text articles were then independently read and following discussion four more articles were excluded (one was a study using animals and three were classified as reviews or commentaries or proceedings) (Table 1). A total of seven articles were selected at this point. Following examination of the reference list of the papers a further four papers were selected that had evaded the electronic search process and following reading and further discussions these were also included. Thus, a total 11 studies were included in this systematic review. Figure 1 summarises the selection process, Table 2 the methodological breakdown of the studies and Table 3 the evaluation of bias.

Methodological bias

The risk of bias of included studies was independently assessed by DS, AC and GM using criteria described in the Cochrane Handbook for Systematic Reviews of Interventions. As reported in Table 3, the majority of studies included in this systematic review have been classified at

potential high risk of bias. This is mostly due to lack of RCT currently available in this topic, which impacted domains such as allocation concealment, blinding of participant, study personnel and outcome assessors.

4 Discussion

4.1. Clinical studies

Dockery (1999) first reported the prospective analysis of 100 patients with intermetatarsal neuroma who had been treated with intra-lesional injections of 4% alcohol and 0.5% bupivacaine hydrochloride with (1:200,000) adrenalin under ultrasound guidance. Each patient received a minimum of three and a maximum of seven injections at 5-10 day intervals. Follow-up after the last injection was between six months and two years. Of the 100 patients 82% reported complete resolution of their symptoms, 7% reported some improvement and 11% reported no improvement. The 11% of patients where the treatment failed were referred for surgery and an enlarged neuroma was reported by pathology for each patient.[9] Although the results for complete resolution of symptoms are good this study has a number of limitations with regards to internal and external validity. The study did not have placebo-control groups, no process of randomisation, no validated outcome measurement tool, some subjects received three injections and others seven, and outcome was recorded at different intervals with some patients reporting at six months and others at two years, hence the reporting could be biased by issues of memory recall and lifestyle modifications. All these issues affect the internal validity. Furthermore, all results were descriptive using percentages and no inferential statistics were used. Thus, this affects the external validity of the study as the results can only be applied to the studied population and not used to generalise the findings to other populations.

A small study of 23 subjects was reported by Masalla et al. (2001) using 30% alcohol and 2% carbocaine hydrochloride with (1:200,000) adrenalin for intra-lesional injections under ultrasound guidance. The study reported a 91% resolution of all symptoms.[45] The methodology for the study was very similar to that used by Dockery (1999) other than the injection interval which was seven days. Hence, the same internal and external validity issues are applicable. The higher complete resolution rate could be related to the use of a higher concentration of alcohol solution.

Fanucci et al. (2004) also used 30% alcohol and 2% carbocaine hydrochloride with (1:200,000) adrenalin for intra-lesional injections under ultrasound guidance. A total of 40 subjects received four injections at 15-day intervals to avoid strong flogistic reactions[1] and follow-up was at ten months.[1] In addition, a ranked outcome measurement tool designed to record outcome for management of intermetatarsal neuroma was used.[46] At ten months follow-up the study reported complete satisfaction for 53% (n=21), 23% (n=9) reported satisfied, but with minor complications, 15% (n=6) were satisfied with major complications, and 10% (n=4) patients were dissatisfied and underwent surgery.[1] The methodological approach of Fanucci et al. (2004) was a great improvement on previous studies although no randomisation, placebo-control groups or inferential statistics were used, thus, affecting the internal and external validity of the findings.

Hyer et al. (2005) studied six patients with eight neuromas with a mean follow-up of 365 days after weekly 3-9 injections of 4% alcohol and 0.5% bupivicaine hydrochloride solution depending on patients. VAS was used to report outcomes and similar results to above were observed.

VAS mean pain reduction was 6.12±3.2 with five of six patients saying they would recommend to a friend as a measure of satisfaction.[47] Apart from the limitations reported above for the other studies this was also a pilot study with a small number of subjects. Overall, the results have low internal and external validity.

A larger study by Musson et al (2012) involving 92 patients, although 12 had treatment for bilateral neuromas, injected 20% alcohol with 0.25% bupivacaine.[48] All neuromas were clinically and sonographically confirmed and all injections were carried out using ultrasound guided technique. After attrition due to incomplete records 75 patients took part in the study. Sixty-six percent (n=55) showed complete or partial relief of symptoms and the treatment was generally well tolerated with only 2% (n=2) of adverse events, although in one case the patient had an allergic reaction. The authors commented that the study design was a limitation because it was retrospective and there was no control group for comparison. However, their study suggested that the size of the lesion was not a significant factor in the outcome of the treatment and hence can be used to treat any neuroma irrespective of size although more evidence is required.

A study, by Mozena et al. (2007) studied 42 subjects (49 intermetatarsal neuromas). All subjects were diagnosed by clinical examination only and received three to seven injections of 4% alcohol and bupivacaine hydrochloride every two weeks with 2-24 months follow-up. Complete resolution was achieved in 33% (n=16) and 29% (n=14) had improved symptoms. Also multiple injections up to a total of five was most effective with 7% (n=3) suffering a flogistic reaction which resolved in two days.[49] This study suggested that the treatment of intermetatarsal neuroma with alcohol injections was not as effective although it also suffered from all the internal and external validity issues mentioned earlier. In addition, none of the intermetatarsal neuromas were confirmed by sonography. A five-year follow-up study using a prospective case series design followed a total of 45 and assessed the effects of ultrasound guided ultrasound alcohol injections.[50] The study concluded that only 29% (n=13) remained symptom free at five-years although 33% were completely satisfied with the treatment and 27% satisfied with a few reservations. A total of 36% (n=16) required excision of the intermetatarsal neuroma. However, it was not clear from the article the concentration of alcohol injections used and number of injections. The authors also acknowledged that some of the data was collected retrospectively which may have led to some bias in reporting. Thus, the evidence presented in this study is also questionable and a more robust methodological design is necessary to inform clinical guidelines.

Hughes et al. (2007) carried out a study in 101 participants with a single lesion. Subjects received a total of three to six intra-lesional injections of 20% alcohol and 0.5% bupivacaine hydrochloride at two week intervals. VAS and a modified scale from Johnson et al. (1988) were used to assess outcome during follow-up at 7-19 months. Seventeen patients (16.8%) reported a flogistic reaction. At baseline, the mean lesion diameter was 10mm (range 7-15mm) and at follow-up 7mm (range 5-11mm) with 84% completely satisfied and pain free with median VAS scores reducing from 8 units to 0 units ($p<0.001$).[10] However, although this is the first study where inferential statistics were used improving the external validity of the study, there are still methodological issues affecting internal validity with regards to no randomisation, no placebo-control groups, non-standardisation of the number of injections used and a big range of time for outcome follow up (7-19 months).

Espinosa et al (2011) carried out a retrospective case series study in an orthopaedic clinical setting of 32 patients following diagnosis of intermetatarsal neuroma.[51] Patients reported the presence of symptoms for a mean of 27 months. Twenty-eight patients had unilateral neuroma and four bilateral. Patients were treated with 20% alcohol and 0.25% bupivacaine using a non-guided technique. Patients were followed up every second week and the injection repeated up to ten times if still symptomatic (66% [n=21/32] received four injections). Mean VAS at baseline was 6.9 and this decreased to 5.2 after four injections. Post hoc analysis showed that seven patients reported a mean VAS of 1.2 by four weeks with the remaining (n=25) reporting a mean VAS of 6.9. Thus, the authors stated the treatment to be effective in 22% (n=7) of cases. The limitations are similar to previous studies with no control use, low number given that it was retrospective and no inferential statistics used in the analysis of the data.

A study by Pasquali et al (2015) evaluating the effectiveness of alcohol injections was carried out in two centres and evaluated a total of 508 patients.[52] The study was a retrospective cross-sectional study and analysed all alcohol injections over an 11 year period. A total of 14.2% (n=72) had bilateral neuromas. All patients were treated with 50% alcohol injections with 2% mepivacaine and had neuromas confirmed both clinically and with diagnostic ultrasound. VAS and patient satisfaction was recorded at the one year follow-up after the injection. Overall, 74.5% were satisfied with the outcome with a reduction in pain and improvements in quality of life. For those patients where the treatment had failed and an alternative treatment offered, 9.3% (n=50) had the neuroma surgically excised.[52] These results suggest a good level of satisfaction with alcohol injections, however the study design was retrospective with no comparisons made with a control group, hence there is a high risk of bias.

The latest study by Perini et al (2016) was a retrospective cohort design with follow-up at 15-24 months of 220 patients (15% [n=33] males and 85% [n=187] females).[53] The mean neuroma diameters were 5.4mm (range 4-9mm). All patients were diagnosed by clinical symptoms confirmed by sonography. Patients received a guided injection using 50% alcohol with 2% lidocaine. Patients received up to three treatments at two week intervals were pain using VAS was evaluated. A complete resolution of symptoms or a reduction of at least 50% of pain using VAS was reported in 72.3% (n=159) $p<0.001$. The results suggest a good and similar level of satisfaction to previous studies although again the research design is retrospective and no comparisons are made with a control group hence there is a high risk of bias. Another aspect of the study to consider is that the average size of the scanned neuromas was small. Thus, an RCT is necessary to draw definitive conclusions about the effectiveness of alcohol injections.

4.1.2 Adverse Events

All the papers in this review, except one[47], reported adverse events post sclerosing alcohol injections for the management of intermetatarsal neuroma. Hyer al al (2005), although no adverse events were reported, one must take into account that this study only included six participants and the concentration of alcohol used was at the lower end of 4%.[47] The other two studies using alcohol concentrations of 4% reported some level of adverse effects that was transient, that is, a flogistic reaction. Dockery (1999), in a study of 100 patients, reported that a common complaint post injection was the feeling of burning but did not present any data for this.[9] In the other study using a concentration of 4%, Mozena et al (2007) reported seven percent of post injection localised pain out of 42 patients that took part in the study.[49]

With regards to studies using alcohol concentrations of 20%, Musson et al (2012) reported post injection local pain in one percent of the 92 patients that took part in this study with another one percent (n=1) reporting a major adverse event of anaphylaxis.[48] Hughes et al (2007) stated that 16.8% of 101 patients in his study suffered a transient local pain post injection with MRI reporting intense mid and forefoot marrow oedema that spontaneously settled after three weeks.[10] In a study with 32 participants, Espinosa et al (2011) reported that nine percent suffered a flogistic reaction.[51]

For alcohol concentrations of 30%, Masala et al (2001) reported a localised transient pain in 78% of 23 patients that took part in the study with a further four percent (n=1) suffering other complications.[45] This was the second highest report of local adverse events of all the paper reviewed. In comparison, Fanucci et al (2004) reported a much lower figure of 15% with regards to local transient adverse events in this study with 40 participants.[1]

At the highest alcohol concentrations of 50%, in a study of 508 participants, Pasquali et al (2015) reported a mean of 0.7 (range 0 to 2) for flogistic reactions.[52] However, although the value appears low making comparison with the other reports for adverse events is difficult. The highest report of adverse events was in the study by Perini et al (2016), the study included 220 participants of which 80.9% reported local short lived pain at the injection site.[53] This was the highest report of adverse events.

Finally, although one study involving 42 participants reported a flogistic reaction in seven percent of cases, the concentration of alcohol used was not reported.[49]

On face validity, for all studies presented, there was no pattern to suggest that using adrenaline with the local anaesthetic agent or guiding the injection had an effect. However, the highest reports of local transient post injection adverse events occurred at alcohol concentrations of 30% and 50%.

Recommendations for clinical practice

Clinicians should note that the research evidence to support alcohol injections is poor as all studies reported in this systematic review suggest a high risk of methodological bias. Until future research studies on the effectiveness of alcohol injections for intermetatarsal neuroma are able to provide robust evidence (for example, by using randomised control trial designs) it is recommended that health professionals consider using a stepwise approach to the management of intermetatarsal neuroma. The management for intermetatarsal neuroma should initially be based on other more evidence based treatments (e.g. steroid injections) prior to trying out this modality of treatment option with alcohol injections. Clinicians should also be aware that the evidence for the most effective percentage of alcohol concentration to inject still needs to be established, however they should note that at higher concentrations there appears to be an increase in adverse events although these are short lived. In addition, when deciding what concentration to use and whether to guide the injections, one should also take note that two animal studies reported no nerve damage regardless of alcohol concentrations used for extra-neural injections. With regards to intra-neural injections, one study reported

no effect up to alcohol concentrations of 30%. The other animal study reported that at alcohol concentrations of 25% a quarter of axons showed neural pathological damage; with alcohol concentrations of 50% signs of pathological nerve damage occurred to half of the axonal tissue in the samples examined.

Recommendations for future research

Randomised control trials comparing the effectiveness of various concentrations of alcohol injections against a control, of for example, the more established treatment of steroid injections are needed. The quality of these studies should be single or double blinded and investigate both short and long-term outcomes prospectively, with adequate power and ideally multi-centred.

5 Conclusion

Following an extensive review of the literature pertaining to the effectiveness of alcohol injections there appears to be some evidence to suggest that alcohol injections as a conservative treatment may be effective in reducing pain levels, quality of life and satisfaction with the treatment. Equally, other studies have suggested that the treatment of intermetatarsal neuroma with alcohol injection may not be effective. Alcohol injections appear to be safe although some studies report a short-term side effect of a flogistic reaction. There are also variances in the alcohol concentration used and guiding verses not guiding the injection using ultrasound imaging. Furthermore, some of the evidence may suggest a sclerosing histological effect of the nerve. However, all the studies reviewed present a research design offering a low level of evidence that is open to methodological biases and interpretation. Thus, this review found insufficient high-quality research evidence to afford conclusions on the management of intermetatarsal neuroma with alcohol sclerosing agent injections.

The management of intermetatarsal neuroma remains a clinical challenge, with steroid injection in the short term supported more strongly by RCTs but long-term management remains an area where more research is required. Given the lack of high level evidence to support the effective management of intermetatarsal neuroma using the current range of reported treatments[22], a staged management approach as recommended by Bennett et al (1995) may be a logical treatment option until further research evidence to support the respective treatment options becomes available [8]. At present, alcohol injections could be included in this stepwise approach but more high-quality evidence is required.

Contribution of Authors

DS, GM and AC drafted the background, the methodology, result, discussion and conclusion sections. All authors read and approved the final version of this manuscript.

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This study received no sources of funding.

Conflict of interest

There were no conflicts of interests.

Competing Interests

DS, GM and AC declare they have no competing interests.

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Figure 1 study selection process.

Table 1 full text articles excluded.

Reference	Reason for exclusion
Morgan et al. (2014)	Systematic Review
Schereiber et al. (2011)	Review
Hetman (2005)	Commentary
Mazoch et al. (2014)	Animal study

*Arbitration by third author (GM) occurred only if a dispute between the two reviewers was not resolved

Table 2 methodological breakdown of the studies.

Author (year)	Study Design	**Intervention**	**Participant number**	**Follow-up period**	**Outcome**	**Adverse events**
Dockery (1999)	Prospective case series	4% alcohol & local anaesthetics with adrenalin No guided injection	100	Mean 13 months (Range 6 months and 2 years)	<u>Satisfaction questionnaire</u> N= (82%) reported complete resolution of symptoms N= (7%) reported some improvement of symptoms N= (11%) reported no improvement of symptoms	No data was presented. The most common complaint was following the first injection with post injection burning sensation, increased ``pins and needles,'' and pain on the ball of the foot in the affected area after anaesthetic effect wore off. This increase in symptoms occurred during the first 48 hours following the first injection and decreased sharply thereafter. No other post injection complications were reported.

Masala et al. (2001)	Prospective case series	30% alcohol & local anaesthetics with adrenalin Guided injection	23	36-48 hours after injection <H1> 3 weeks 7 weeks	<u>Satisfaction questionnaire</u> N=21 (91%) reported complete resolution of symptoms [n=3 complete resolution within 3 weeks; n=5 complete resolution within 40-50 days] N=2 (9%) reported no improvement of symptoms	N=18 (78%) pain at injection site that disappeared within 3-4 days. N=1 (4%) other procedure related complications reported.	
Fanucci et al. (2004)	Prospective case series	30% alcohol & local anaesthetics Guided injection	40	10 months	<u>Johnson Scale</u> N=21 (53%) reported complete satisfaction with treatment N=9 (23%) reported satisfied, but with minor complications N=6 (15%) were satisfied, but with major complications N=4 (10%) were dissatisfied and underwent surgery	N=6 (15%) transitory plantar pain, due to the flogistic reaction. No other procedure related complications was reported.	
Hyer et al. (2005)	Prospective case series	4% alcohol & local anaesthetics with adrenalin No guided injection	6	Mean 346±50.3 days	<u>Pain VAS</u> Mean pain reduction 6.13±3.2 <u>Satisfaction questionnaire</u> N=5 (83%) would recommend procedure to a friend	No adverse events with the injections was reported.	

Musson et al. (2012)	Prospective case series	20% alcohol & local anaesthetics Guided injection	92	Mean 14.3 months (Range 6-26 months)	<u>Pain VAS</u> Median pain VAS pre-procedure 8 (range 4-10) Median pain VAS post-procedure 4 (range 0-10) <u>Satisfaction questionnaire</u> Of 85 treatment courses with 2 patients excluded for multiple neuromas: N=55 (66%) reported complete/partial resolution of symptoms [of these n=27 had complete resolution and n=28 partial resolution] N=30 (35%) reported no improvement	N=1 (1%) developed an allergic reaction with facial swelling and vomiting soon after the first treatment. N=1 (1%) found injection very painful and declined further treatment. N=1 (1%) developed significant pain and swelling following the second injection so the third treatment was delayed by one week. There were no other complications and all other patients tolerated the treatment well.
Mozena et al. (2007)	Prospective case series	4% alcohol & local anaesthetics with adrenalin No guided injection	42	Mean 11 months (Range 2-24 months)	<u>Satisfaction questionnaire</u> N=16 (33%) reported complete resolution of symptoms N=14 (29%) reported an improvement of symptoms.	N=3 (7%) reported a post injection short-term complication, two complained of pain that resolved within the first 24 hours, and one had some erythema around the injection area that resolved within 2 days. No other procedure related complications was reported.

Gurdezi et al. (2013)	Prospective case series	Alcohol concentration not reported. Also use of local anaesthetic or adrenalin was not reported Guided injection	45	Mean 5 years (range 2.75-6 years)	<u>Pain VAS</u> Pain VAS pre-procedure 8[a] Pain VAS post-procedure 4[a] **<u>Pain rate</u>** N=13 (29%) reported pain free N=18 (40%) reported mild/moderate pain N=14 (31%) reported no difference <u>Modified Johnson score</u> N=15 (33%) reported complete satisfaction with treatment N=12 (27%) reported satisfied, but with minor reservations N=5 (11%) were satisfied, but with major reservations N=9 (9%) were dissatisfied N=4 (9%) I wish I had never had the injection	N=12 (27%) reported complications. N=9 (20%) reported immense pain at the time of injection, despite local anesthetic infiltration. N=3 (7%) had extensive bruising at the injection site, and N=2 (4%) complained of ongoing numbness of the toes.	
Hughes et al. (2007)	Prospective case series	20% alcohol & local anaesthetics	101	Mean 10.5 months (Rang	<u>Pain VAS</u> Median Pain VAS pre-procedure 8 (interquartile range 7-8)	N=17 (16.8%) reported plantar pain that settled after 2 days–3 weeks (mean, 4.5 days). In one such case, post procedural MRI showed intense mid- and forefoot	

		Guided injection		e 7-19 months)	Median Pain VAS post-procedure 4 (interquartile range 0-1) **<u>Pain rate</u>**[b] N=84 (84%%) reported pain free N=8 (8%%) reported mild/moderate pain N=8 (8%) reported no difference <u>Modified Johnson score</u>[b] N=62 (62%) reported complete satisfaction with treatment N=24 (24%) reported satisfied, but with minor reservations N=5 (5%) were satisfied, but with major reservations N=3 (3%) were dissatisfied N=6 (6%) I wish I had never had the injection	marrow oedema that spontaneously settled after 3 weeks. No other procedure related complications was reported.

Pasquali et al. (2015)	Retrospective case series	50% alcohol & local anaesthetics Guided injection	508	1 year	<u>Pain VAS</u> Mean Pain VAS pre-procedure 8.7 (range 6-10) Mean Pain VAS post-procedure 3.6 (range 0-9) <u>Satisfaction questionnaire</u>[c] N=137 feet (25.3%) VAS Score 0 N=263 feet (48.7%) VAS Score 1-3 N=140 feet (25.9%) little or no resolution of symptoms[c]	Mean local inflammatory reaction was 0.7 (range, 0 to 2). There were no other local or systemic complications.
Perini et al. (2016)	Retrospective case series	50% alcohol & local anaesthetics Guided injection	220	Mean 19 months (range 15-24 months)	<u>Pain VAS</u> Median Pain VAS pre-procedure 9 (interquartile range 8-10) Median Pain VAS post-procedure 3 (interquartile range 0-6) <u>Satisfaction questionnaires</u> N=159 (72.3%) complete resolution of symptoms or a reduction of at least 50% of pain using VAS N=28 () complained of neuropathic pain	N=178 (80.9%) short-living pain on the injection site was a constant complaint. No other procedure related complications was reported.

					N=33 () complained of mixed neuropathic and nociceptive pain <u>Limitation of daily living scale (score 0-3)</u> Median pre-procedure 3 (interquartile range 2-3) Median post-procedure 0 (interquartile range 0-0)	
Espinosa et al. (2011)	Retrospective case series	20% alcohol & local anaesthetics No guided injection	32	Range 2-20 weeks	<u>Pain VAS</u> Mean Pain VAS pre-procedure 6.9 (range 4-10) Mean Pain VAS post-procedure 5.2 (range 0-10) <u>Satisfaction with treatment</u>[d] N=7 (22%) reported successful treatment	N=3 (9%) developed a transient intolerable pain from the local infiltration of alcohol and bupivacaine and did not receive the full 1-ml injection. No major complications, were reported.

[a] Authors did not report if the VAS score was the mean or median.

[b] One patient could not be contacted.

[c] No VAS score given

[d] No validated satisfaction tool was used.

Table 3 risk of bias in selected studies.

RISK OF BIAS								
AUTHORS	DOMAIN							
	SEQUENCE GENERATION	**ALLOCATION CONCEALMENT**	**BLINDING OF PARTICIPANTS**	**BLINDING OF PERSONNEL**	**BLINDING OF OUTCOME ASSESSORS**	**INCOMPLETE OUTCOME DATA**	**SELECTIVE OUTCOME REPORTING**	**OTHER SOURCES OF BIAS**
Dockery (1999)	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**UNCLEAR**	**UNCLEAR**
	Not randomly assigned	No allocation concealment performed	Participants were not blinded	Study personnel were not blinded	Outcome assessor were not blinded	'Excluded from the study where any patient that discontinued therapy prior to the 3rd injection''	No reference to study protocol	No other sources of bias reported *(ie: conflict of interest)*
Masalla et al. (2001)	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**UNCLEAR**	**UNCLEAR**	**UNCLEAR**
	Not randomly assigned	No allocation concealment performed	Participants were not blinded	Study personnel were not blinded	Outcome assessor were not blinded	Unclear	Unclear	Unclear
	HIGH RISK	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**LOW RISK**	**UNCLEAR**	**UNCLEAR**

Fanucci et al.(2004)	Not randomly assigned	No allocation concealment performed	Participants were not blinded	Study personnel were not blinded	Outcome assessor were not blinded	``Total of 160 injections were performed in 40 patients'' All cases were accounted in the provided outcome data	No reference to study protocol	No other sources of bias reported *(ie: conflict of interest)*
	HIGH RISK	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**UNCLEAR**	**UNCLEAR**
Hyer et al. (2005)	Not randomly assigned	No allocation concealment performed	Participants were not blinded	Study personnel were not blinded	Outcome assessor were not blinded	``Of the initial 8 patient eligible for this study, 2 patients (6 neuromas) were lost to final follow up''	No reference to study protocol	No other sources of bias reported *(ie: conflict of interest)*
	HIGH RISK	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**UNCLEAR**	**UNCLEAR**
Musson et al (2012)	Not randomly assigned	No allocation concealment performed	Participants were not blinded	Study personnel were not blinded	Outcome assessor were not blinded	``Seventeen patients has incomplete pre-treatment and follow-up data, and were therefore excluded''.	No reference to study protocol	No other sources of bias reported *(ie: conflict of interest)*
	HIGH RISK	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**LOW RISK**	**UNCLEAR**	**UNCLEAR**
Mozena et al (2007)	Not randomly assigned	No allocation concealment performed	Participants were not blinded	Study personnel were not blinded	Outcome assessor were not blinded	All selected cases were accounted and reported in the results section.	No reference to study protocol	No other sources of bias reported *(ie: conflict of interest,*
	HIGH RISK	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**UNCLEAR**	**LOW RISK**

Gurdezi et al. (2013)	Not randomly assigned	No allocation concealment performed	Participants were not blinded	Study personnel were not blinded	Outcome assessor were not blinded	``60 patients had ultrasound guided alcohol injection for Morton's neuroma between March 2004 and June 2007 at our institution. 45 of this patients were available for follow up''	No reference to study protocol	``Authorship declared no conflict of interest with respect to research authorship and publication of the article''.
Hughes et al. (2007)	**HIGH RISK** Not randomly assigned	**HIGH RISK** No allocation concealment performed	**HIGH RISK** Participants were not blinded	**HIGH RISK** Study personnel were not blinded	**HIGH RISK** Outcome assessor were not blinded	**LOW RISK** 100 patients were contacted, but 1 patient could not be contacted''	**UNCLEAR** No reference to study protocol	**UNCLEAR** No other sources of bias reported *(ie: conflict of interest)*
Pasquali et al. (2015)	**HIGH RISK** Not randomly assigned	**HIGH RISK** No allocation concealment performed	**HIGH RISK** Participants were not blinded	**HIGH RISK** Study personnel were not blinded	**HIGH RISK** Outcome assessor were not blinded	**UNCLEAR** Unclear as resulted were presented as number of treated feet rather than number of treated patients at 1 year follow up.	**UNCLEAR** No reference to study protocol	**LOW RISK** ``Authorship declared no conflict of interest with respect to research authorship and publication of the article''.
Perini et al. (2016)	**HIGH RISK** Not randomly assigned	**HIGH RISK** No allocation concealment performed	**HIGH RISK** Participants were not blinded	**HIGH RISK** Study personnel were not blinded	**HIGH RISK** Outcome assessor were not blinded	**HIGH RISK** `` 7 patients for incomplete dataset'' were excluded.	**UNCLEAR** No reference to study protocol	**LOW RISK** ``Authorship declared no conflict of interest with respect to research authorship and publication of the article''.

	HIGH RISK	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**HIGH RISK**	**UNCLEAR**	**UNCLEAR**	**LOW RISK**
Espinosa et al. (2011)	Not randomly assigned	No allocation concealment performed	Participants were not blinded	Study personnel were not blinded	Outcome assessor were not blinded	Unclear	No reference to study protocol	``No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article''.

1A number of authors refer to a flogistic reaction but do not define what they mean by this. To clarify this a flogistic reaction will be taken as an inflammatory local response to injection with transient pain.