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Review

Effectiveness of corticosteroid injections in Civinini–Morton's Syndrome: A systematic review

Elena Samaila[a,1], Gabriele Colò[b,1], Alessandro Rava[c], Stefano Negri[a], Roberto Valentini[a], Lamberto Felli[b], Bruno Magnan[a,*]

[a] Department of Orthopedics and Trauma Surgery, University of Verona, Italy
[b] Orthopaedic Department, University of Genova, Italy
[c] Department of Orthopaedic and Traumatology, University of Turin, Italy

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ABSTRACT

Background: The aim of this paper is to analyze the effectiveness of corticosteroid injections (CI), in combination with or without a local anaesthetic, for Civinini–Morton's Syndrome to determine which protocol could be the most appropriate among conservative treatments.
Methods: All selected articles were screened using a thorough database search of PubMed, EMBASE and SCOPUS to assess their suitability to the research focus.
Results: Selection produced 10 articles as full-text, for a total of 590 patients, with a mean follow-up of 14 ± 14.2 (range 3–48) months. Johnson satisfaction scale, resulting from 6 studies, scored 25.6% (range 5–38) and 39.4% (range 15–51.8), respectively completely satisfied and satisfied with minor reservations. Mean VAS, declared in 5 studies, decreased from 70.7 ± 16.5 (range 67–89) to 33.4 ± 7.6 (26–42.5) points ($p < 0.01$). Most common complication was skin depigmentation in 7 (2.6%) cases.
Conclusions: CI appear to be a safe treatment allowing good results with a very low complications rate. A neuroma of 6.3 mm seems to be the cut-off size; below which CI could have best indications and be considered as an intermediate treatment between shoe modifications and more invasive procedures such as percutaneous alcoholization or surgery.
Level of evidence: Level II, systematic review.

Contents

* Corresponding author at: Department of Orthopedics and Trauma Surgery, University of Verona, Surgical Center "P. Confortini", P.le A. Stefani, 1, 37126 Verona, VR, Italy.
E-mail address: bruno.magnan@univr.it (B. Magnan).
[1] These authors contributed equally to this work.

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1. Introduction

Morton's neuroma is a frequent forefoot pain condition, affecting mainly middle-aged females with a ratio female:male ≥5:1 [1–5]. The pathology originates from the common digital plantar nerves and strikes mainly in the third inter-metatarsal space (IMS), followed as incidence by the second, known as Hauser's Neuroma [6]; localization in the first and fourth IMS is extremely rare [7].

Civinini Morton's Syndrome (CMS), the more correct terminology as Pisani suggests [8], causes an important interdigital neuropathic pain.

Surgical treatment has been considered the gold standard and it is still widely used [9]. Other treatment managements as cryogenic neuroablation have been also proposed [10], with a success rate similar to surgical excision.

Among non-surgical treatments for CMS, in the last decades satisfactory clinical results through percutaneous alcohol injection under ultrasound guidance (USG) [11] and percutaneous electro-stimulation-guided alcoholization with phenol [12,13] have been reported. Nevertheless, corticosteroid injection (CI) is considered the first-choice treatment, with better results than other conservative treatments such as shoes modification [3] and anaesthetic injections alone [14], this latest, often used also as diagnostic "block" test [15]. Several studies with discordant results with CI are reported in the literature [1,3] and different modifications, such as the use of a corticosteroid combined with a local anaesthetic [16] or using USG during the procedure [17], are still debated.

No reviews assessing the effectiveness of corticosteroid injections for CMS have been published yet in the literature; therefore, the aim of this study was to systematically analyse the available literature relating the evidence base of CI in patients affected by CMS.

2. Materials and methods

The following data are the result of a thorough search of useful literature on PubMed, Google Scholar, Embase, Medline and Medscape. The PRISMA 2009 flow chart and checklist were considered to revise the paper [18]. To identify studies relating to corticosteroid injections of CMS, a clinical question was defined using the population, intervention, comparison, outcome and study type (PICOS) format prior to establishing the search strategy. Population was defined as adults aged 18 years or older with a CMS diagnosed through clinical symptoms, sonography or magnetic resonance imaging, without a history of significant trauma, foot surgery or systemic inflammatory conditions. Intervention was defined as any non-surgical corticosteroid injection, with the exclusion of alcohols and phenol, that aimed to reduce pain associated with CMS. Authors utilized different combinations of the following keywords: Morton, neuroma, Civinini, steroid injection, interdigital nerve. Two authors (G.C. and A.R.) independently examined titles and abstracts of all the identified articles to evaluate their inherent research focus. The full-text of the selected documents were then evaluated. References from identified articles have been verified for do not missing any relevant items. Inclusion criteria were: studies related to correct indications, management and clinical outcomes of corticosteroid injections in patients affected by CMS; retrospective or prospective clinical studies including randomized and non-randomized controlled trials (RCTs), case series, cohort studies and case-control studies; papers in English without any restriction on publication year. The exclusion criteria were: articles that did not provide data related to correct indications, management and clinical outcomes of corticosteroid injections in patients affected by CMS; experimental biomechanical or cadaveric studies; review, meta-analysis, single case report and non-English written articles. Studies that provided data related to injections for CMS but not specifically related to CI were even excluded (Fig. 1).

When available, the following data were obtained from the individual articles: first author, year of publication, study design, number of patients (divided by groups in case of controlled studies), average age of patients (years), type of procedure performed, number of injections, average follow-up (FU) (months), IMS affected, complications, need of surgery or further injections and clinical evaluation. Studies that did not declare a specific variable were excluded from the global assessment of that variable; categorical data were expressed as number of cases or percentage. Continuous variables were referred as mean and standard deviation (SD) or mean and interval. The Level of Evidence (LOE) of the studies was assigned based on the Evidence Based Evidence Center of the Oxford Center for Evidence [19].

3. Results

3.1. Demographics

The selection produced a total of 10 articles regarding the correct indications, management and clinical outcomes of corticosteroid injections in patients affected by CMN (Table 1).

Included studies encompassed a total of 713 patients (794 feet) and 590 among them underwent CI plus anesthetic or corticosteroid alone. The remaining 123 patients did not perform CI or were used as control groups. These patients were not included in the data analysis.

For the studies that declare it [1,3,14,16,17,20–23], 549 were females (81.1%) and 128 were males (18.9%). Only one author [24] describes 33 female feet and 12 male feet. The average age of patients at time of injections was 54.5 ± 2.4 (range 51.9–58.1) years. The mean follow-up was 14 ± 14.2 (range 3–48) months.

Studies took place in United States of America (1 study) [21], Turkey (1 study) [3], United Kingdom (3 studies) [14,22,24], Australia (2 study) [1,20], Spain (2 studies) [16,17] and Korea (1study) [23]. The studies consisted in five randomized clinical trials (RCTs) [3,14,16,17,24] and five case series (CS) [1,20–22].

According to the Oxford level of evidence scale [25], level of evidence was rated as 2 in five cases and 4 in the other studies.

3.2. Interspace involved

The sites of treated neuromas were reported only in six articles [1,3,6,16,17,21] describing 386 patients. The third IMS was affected in 280 (72.5%) cases, the second in 84 (21.8%), while only in 27 (7%) cases the interspaces were both treated. In 204 patients [14,20,22,24] the IMS affected was not specified.

3.3. Diagnosis

The diagnostic protocol used was not uniform in the analysed studies. Most authors utilized a clinical evaluation and an instrumental confirmation before injections [1,14,16,17,22,23],

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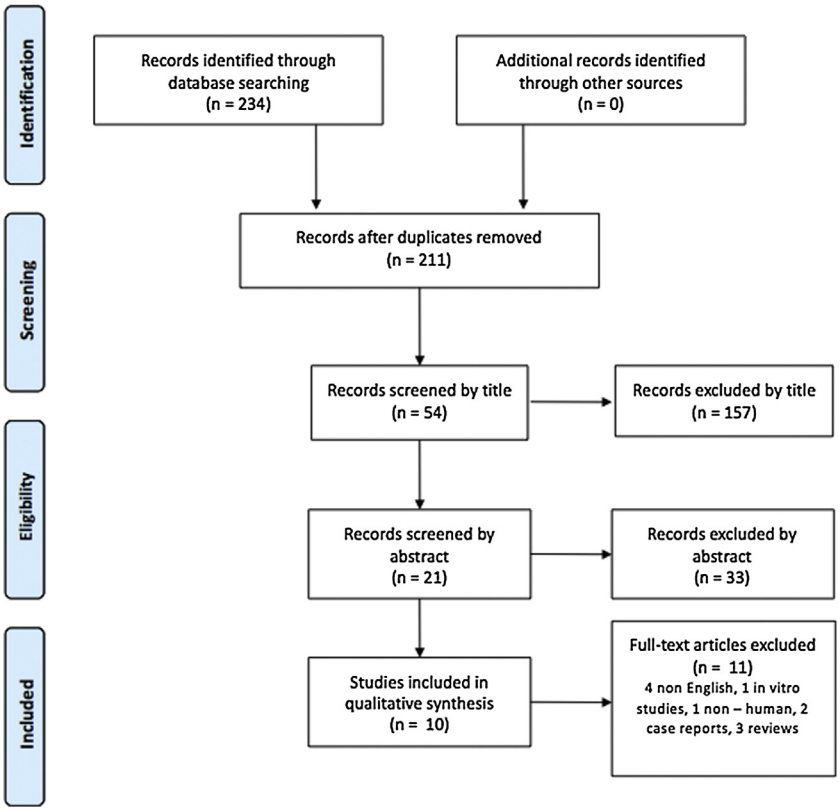

Fig. 1. The PRISMA flow chart illustrates the number of studies examined, included and excluded, as well as the reason for the exclusion.

while in 3 studies authors used only a clinical diagnosis [3,20,21]. The diagnostic methods were described in detail in 8 studies, for a total of 470 patients [1,3,16,20–24]. Physical examination findings were reported in 100% of cases, in which were evaluated Mulder's click in 470 patients (100%), palpable pain in 426 (90.6%), IMS sensory loss in 252 (67.5%), interspace tenderness in 148 (31.5%), metatarsalgia and swelling in 44 (9.4%). Medical history of patients was evaluated in 99 cases (21,1%) including pain magnitude, location, intensity and restrictions of activity [16,21,22]. Imaging tools were utilized in 7 studies, enclosing 447 patients [1,14,16,23,17,22–24]: in 431 cases (96.5%) sonographic confirmation was used, while in 16 patients (3.5%) the diagnosis was confirmed by Magnetic Resonance Imaging (MRI). In only 39 cases (8.7%), patients were also evaluated by conventional X-ray [22]. Two authors declare physical examination with US confirmation [14,17], without specifying the detail of clinical procedure.

3.4. Injection procedure

Injections of corticosteroid plus anaesthetic were compared with footwear modifications in only 1 study [3]. Two RCT studies compared injections of corticosteroid plus anaesthetic free-hand performed and USG technique [17,24]. Injections of corticosteroid plus anaesthetic were compared to anaesthetic alone injections by two RCT's [14,16]. The remaining five studies were case series reporting results obtained with corticosteroid plus anaesthetic injections [1,20–23].

Different combinations of steroid and local anaesthetic were adopted. Association of corticosteroid and local anesthetic have proved advantages when compared to anesthetic alone in only one of the 2 RCT which considered these different options [14,16]. In the remaining, the addition of anaesthetic to steroid reported controversial results. Full details on drugs and dosage are reported in Table 1.

There were other differences between protocols employed by authors. In 5 studies [1,14,21,23,24] only 1 injection was performed, except for one study in which authors performed up to 3 injections in patients with persistent pain [23]. Three injections were performed in 3 studies [3,16,27]. Greenfield states one up to more than four, with a mean of 3.07 injections in all patients, without specifying how many of them received in detail the injections [20]. Ruiz [20] declared an average number of injections of 2,4 ± 0,2. One study did not specify the protocol performed [23]. The total average of injections, for the studies that declare it [1,3,14,16,17,20,21,24], was 1,5 ± 0,8.

The injection technique was not uniform in the analysed studies. Free-hand technique was used by 3 authors [3,20,21] while USG injection was utilized in most cases [1,14,22,23]. No differences can be found at FU between free-hand and USG techniques [17,24]. In 2 studies [17,24] both techniques were performed but the different techniques were not compared. For the remainder [16], the utilized technique was not reported.

The injection approach was narrowly described in 7 studies [1,14,17,20,21,23,24]. Authors reported a dorsal approach in most cases [17,20,21,23,24], one author performed CI by a plantar approach [14], while another author describes distal to proximal injections [1].

3.5. Size of neuromas

The size of neuromas, intended as transverse diameter, was described in 6 studies [1,14,16,17,23,24], for a total of 408 cases. Authors reported an average size of 7.5 ± 0.7 mm. One author considered indicated CI in patients with neuromas sized more than 5 mm [14]. No lesion size was declared in the other studies [3,20–22].

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Table 1
The main features of the included studies are summarized. AOFAS: American Orthopaedic Foot & Ankle Score; FHT: Foot Health Thermometer; LOE: level of evidence; MFPDS: Manchester Foot Pain and Disability Schedule; MFPDS pr: Manchester Foot Pain and Disability Schedule pain related; MFPDSwd: Manchester Foot Pain and Disability Schedule walking/doing; MFPDSwa: Manchester Foot Pain and Disability Schedule work/activities; MOxFQ-Index: Manchester-Oxford Foot Questionnaire Index; VAS: Visual Analogue Scale; MRI: Magnetic Resonance Imaging.

Authors and years	Study design and level of evidence (LOE)	Number of patients (F:M)/feet	Mean patients age (years)	Diagnosis	Size of neuromas	Interspace involved	Type of injection procedure and technique	Number of injections	Follow-up (months)	Complications	Clinical evaluation and final average score	Required surgery or/and further injections (%)
Greenfield et al. (1984) [20]	Case series (IV)	Total study:67 (52:15)/67; 65 steroids injections, 2 shoe modifications	58 (range 19–85)	Physical examination findings	Not specified	Not specified	Xylocaine 1% + 1cc of Steroid (Prednisolone, Betamethasone or Triamcinolone) - Free-hand technique (dorsal approach)	1 (up to 4) with a mean of 3.07	24	Not specified	Self-reported relief pain: • relieved pain in 35/59 (59,3%) • partial relief in 17/59 (28,8%) • no improvement in 7/59 (11,9%)	11 patients (7%) required surgery
Rasmussen et al. (1996) [21]	Case series (IV)	Total study: 44 (29:14)/51	53 (range 24–77)	Medical history and physical examination findings	Not specified	3rd (100%)	1 mL of Betamethasone +1 mL of 0.5% Bupivacaine - Free-hand technique (dorsal approach)	1	48 (24–72)	None	Johnson satisfation scale: • completely satisfied 19/50 (38%) • satisfied minor reservations 9/50 (18%) • satisfied major reservations 10/50 (20%) • dissatisfied 12/50 (24%); Mann scale, 26/50 (52%): • reported less than 50% improvement • 24/50 (48%) reported greater than 50% improvement	24 feet (47%) required surgery
Saygi et al (2005) [3]	Randomized clinical trial (II)	Total study: 69 (60:9)/71; Group 1 (footwear modifications): 35 (31:4)/71; Group 2 (steroid injections): 34 (29:5)/35	Group 1: 51.97 ± 11.80; Group 2: 51.88 ± 10.97	Physical examination findings	Not specified	2nd: 5 (14.3%); 3rd: 27 (77.1%); both: 3 (8.6%)	Methylprednisolone acetate (40 mg) + Prylocaine Hcl (40 mg) - Free-hand technique (approach not specified)	2	12	Not specified	Self-reported satisfaction: • 82% completely satisfied • 6% satisfied with discomfort • 12% dissatisfied	Not reported
Hassouna et al. (2007) [22]	Case series (IV)	39 (32:7)/39	55.8 ± 13.4 (range 26–83)	Medical history, physical examination findings, ultrasound and X-ray confirmation	Not specified	Not specified	Triamcinolone (20 mg) + Bupivacaine 2 mL 0.5% - Ultrasound guided technique (approach not specified)	Not specified	11.4	None	Self-reported relief pain: • 28% complete pain relief • 26% mild pain • 28% moderate pain • 18% severe pain; Johnson satisfaction scale: • 31% completely satisfied • 15% satisfied with minor reservetions • 13% satisfied with major reservetions • 41% dissatisfied	3/39 (7.7%) required surgery)

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Markovic et al. (2008) [1]	Case series (IV)	35 (28:7)/39	54 (range 29–77)	Physical examination findings and ultrasound confirmation	7.3 (range 5–11) mm	2nd: 8 (20.5%); 3rd: 31 (79.5%)	Betametasone 5.7 mg + 0.5 cc of 1% Lidocaine - Ultrasound guided technique (distal to proximal approach)	1	9	None	Lower extremity functional scale: • 28% complete pain relief • 44% mild pain (at 1 month) • 31% non responder to conservative treatment; Johnson satisfaction scale: • 38% completely satisfied • 28% satisfied with minor reservetions • 17% satisfied with major reservetions • 17% dissatisfied	12/39 (31%) required surgery
Thomson et al (2013) [14]	Randomized clinical trial (II)	Total study: 131 (111:20)/190; Group 1 (steroid + anesthetic): 64; Group 2 (anesthetic alone): 67	53	Physical examination findings and ultrasound confirmation	≥5 mm	Not specified	1 mL methylprednisolone acetate (40 mg) +1 mL 2% Lignocaine or 2 mL 1% Lignocaine alone - Ultrasound guided technique (plantar approach)	1	12	5% skin depigmentation (or atrophy of the plantar fat pad) in Group 1	FHT: • Group 1: 64.7 ± 22 • Group 2: 50.9 ± 27.2; VAS: • Group 1: 44.5 ± 23.3 • Group 2: 51.5 ± 24.6; MFDSpr: • Group 1: 35.5 ± 23.5 • Group 2: 39.8 ± 23.2; MFDSpd: • Group 1: 30.5 ± 21.5 • Group 2: 41.9 ± 26.3; MFDSpa: • Group 1: 18.9 ± 23.1 • Group 2: 25.9 ± 27.5	Group 1: 19/60 (32%) required surgery; Group 2: 28/65 (43%) required surgery
Mahadevan et al (2016) [24]	Randomized clinical trial (II)	Total study 36/45 (33 female feet and 12 male feet); Group 1: (Ultrasound guided): 23 feet; Group 2 (Free-hand technique): 22 feet	Group 1: 57.1 ± 11.7; Group 2: 58.6 ± 14.3	Physical examination findings and ultrasound confirmation	Group 1: 10 (range 9.5–14) mm Group 2: 11 (range 9-12) mm	Not specified	Triamcinolone (40 mg) +2 mL 1% Lignocaine - Ultrasound guided or free-hand technique (dorsal approach)	1	12	4.5% skin depigmentation in Group 2	VAS, MOxFQ-Index were not statistically significant at all time-points; Johnson satisfaction scale at 3 months: Group 1: • completely satisfied 30.5% • satisfied with minor reservation 39% • satisfied with major reservation 4.5% • dissatisfied 26%; Group 2: • completely satisfied 5% • satisfied with minor reservation 45% • satisfied with major reservation 23% • dissatisfied 27%; Johnson satisfaction scale at 12 months was similar in the 2 groups	23/45 feet (51%) (31% required surgery, 20% further injection)
Lizano-Diez et al (2017) [16]	Randomized clinical trial (II)	Total study 35/35; Group 1 (steroid + anesthetic): 16	Group 1: 57.7 ± 9.8; Group 2:	Medical history, physical examination findings	Group 1: 0.8 ± 0.2 cm Group 2:	Group 1 2nd: 6 (17.1%); 3rd: 10 (28.6%)	Group 1: 1 mL Triamcinolone (40 mg) +1 mL Mepivacaine 2%; Group 2: 2 mL	3	6	Not specified	VAS, AOFAS and Johnson satisfaction scale scores showed no differences between groups;	17/35 (48.5%) required surgery: Group 1: 7 (44%);

Table 1 (*Continued*)

Authors and years	Study design and level of evidence (LOE)	Number of patients (F:M)/feet	Mean patients age (years)	Diagnosis	Size of neuromas	Interspace involved	Type of injection procedure and technique	Number of injections	Follow-up (months)	Complications	Clinical evaluation and final average score	Required surgery or/and further injections (%)
		(12:4); Group 2 (anesthetic alone): 19 (17:2)	60.7 ± 11.6	and MRI confirmation	0.8 ± 0.2 cm	Group2: 2nd: 2 (5.7%); 3rd: 17 (48.6%)	Mepivacaine 2% - Technique not specified (approach not specified)				Johnson satisfaction scale: Group 1: • 37.5% completely satisfied • 25% satisfied with minor reservetions • 19% satisfied with major reservetions • 18.5% dissatisfied; Group 2: • 32% completely satisfied • 26% satisfied with minor reservetions • 16% satisfied with major reservetions • 26% dissatisfied	Group 2: 10 (53%)
Park et al (2017) [23]	Case series (IV)	Total study 201 (158:43)/201 Group 1 (no further treatment): 161; Group 2 (need further treatment): 40	55.9 (range 23–80)	Physical examination findings (palpable pain, sensory loss in the web space, Mulder's click) and ultrasound confirmation	Group 1: 4.9 (range 3.3–8.0) mm Group 2: 9.1 (range 4.8-17.0) mm	2nd: 57 (28.4%); 3rd: 144 (71.6%)	1 mL Dexamethasone (5 mg) and 1 mL 1% Lidocaine - Ultrasound guided technique (dorsal approach)	1 (up to 3)	6	Not specified	VAS: 2.6 (8.9 at start) Johnson satisfaction scale: • 20.4% completely satisfied • 51.8% satisfied with minor reservetions • 12.9% satisfied with major reservetions • 14.9% dissatisfied	40/201 (19.9%) required surgery
Ruiz Santiago et al (2018) [17]	Randomized clinical trial (II)	Total study 56 (50:6)/56: Group 1 (Free-hand): 27; Group 2 (Ultrasound guided technique): 29	Group 1: 50.3 ± 1.6; Group 2: 54.1 ± 2.7	Physical examination findings and ultrasound confirmation	Group 1: 4.2 ± 0.3 mm; Group 2: 5.5 ± 0.4 mm	2nd: 8 (14.3%); 3rd: 24 (42.8%); both: 24 (42.8%)	Triamcinolone (40 mg) +1 mL 2% Mepivacaine - Free-hand or ultrasound guided technique (dorsal approach)	Group 1: 2.7 ± 0.2; Group 2: 2.1 ± 0.1	6	Group 1: • 5/27 (18,5% skin de-pigmentation); Group 2: • 1/27 (3.7% skin de-pigmentation) • 1/27 (3.7% local hypersensitivity) • 1/27 (3.7% crossover toe)	VAS and MFPDS showed no significative differences at 6 months; Group 2 proved better results for the first 3 months	Not reported

Table 2
Level of Johnson Satisfaction Scale (JSS) after treatment (386 patients).

	Completely satisfied	Satisfied minor reservations	Satisfied major reservations	Dissatisfied
Patient (n/tot)	99/386	152/386	56/386	79/386
Percentage % (range)	25.6% (5–38)	39.4% (15–51.8)	14.5% (10–19)	20.5% (14.9–41)

3.6. Clinical and functional outcomes

Clinical evaluation at FU was described in all the studies [1,3,14,16,17,20–24]. Different combinations of functional evaluation scales were used. Authors declared: Johnson Satisfaction Scale (JSS) in 386 (65.4%), Visual Analogue Scale (VAS) in 373 (63.2%) patients, Manchester Foot Pain and Disability Schedule (MFPDS) in 120 (20.3%), Self-reported relief pain in 98 (16.6%), Lower extremity functional scale in 35 (5.9%), Self-reported Satisfaction (SRS) in 34 (5.8%), Foot Health Thermometer (FHT) in 64 (10.8%), Mann scale in 44 (7.5%), Manchester-Oxford Foot Questionnaire (MOxFQ) Index in 36 (6.1%) and American Orthopaedic Foot & Ankle Score (AOFAS) in 16 (2.7%).

JSS, used in most studies [1,16,21–24], showed 25.6% (range 5–38) and 39.4% (range 15–51.8) of patients respectively completely satisfied and satisfied with minor reservations. Details of JSS are reported in Table 2.

VAS scores were declared only in 5 studies [14,16,17,23,24]; pre- and post CI scores were compared using T-Student test. A $p < 0.01$ was considered statistically significant. Mean VAS decreased from 70.7 ± 16.5 (range 67–89) to 33.4 ± 7.6 (26–42.5) points ($p < 0.01$). Full details of clinical outcomes with all the considered evaluation scores are reported in Table 1.

3.7. Complications

Complications were reported in 6 studies [1,14,17,21,22,24], including 264 patients: skin depigmentation in 7 cases (2.6%), local hypersensitivity and crossover toe in 1 (0.4%). Thomson [14] observed a skin depigmentation or atrophy of the plantar fat pad in 5 patients (1.9%), without specifying which of them had one or both adverse effects. For the remainders [3,20,16,23] complication findings were unknown.

3.8. Further interventions

In 8 studies, for a total of 588 patients, further procedures were required in 139 cases (23.6%) [1,14,16,20–24]: excision surgery in 130 cases (22.1%), further CI, in addition to own protocol, in 9 (1.5%). For two authors [3,17] no other interventions were required.

4. Discussion

CMS is not really a neuroma, but a perineural fibrosis with vascular proliferation and intraneural sclerohyalinosis of the common digital nerve, causing an important interdigital neuropathic pain [26]. Therefore, some authors, as Weinfield and Myerson, proposed the more correct term of “interdigital neuritis” [27].

The condition was first recognized as a specific anatomical-entity by the Italian anatomist Filippo Civinini in 1835 [28], during a cadaveric dissection, and clearly described in his anatomic letter entitled “On the neural gangliar swelling of the foot sole". Subsequently, the English surgeon Lewis Durlacher in 1845 [26] described it as "a form of neuralgic condition affecting the plantar nerve between the third and fourth metatarsal bone". This last description better respects current pathogenic concepts. Finally, in 1876 the American surgeon Thomas G. Morton [4] wrongly attributed the symptoms to subluxation of the fourth metatarsophalangeal (MTP) joint, proposing its excision. Thus, even if the term came commonly into use in the 19th century, the attribution to Morton is not correct from a pathological point of view. For these reasons, since the designation to Morton is widely used, the more correct terminology should be “Civinini–Morton Syndrome” [8].

The common plantar digital nerves are final branches of the medial and lateral plantar nerves passing from the plantar webspace beneath the intermetatarsal ligaments. Each common digital nerve run within the plantar aponeurosis and splits into 2 branches providing the plantar skin of the toes. Smaller ramifications provide innervation to the adjacent metatarsals, MTP joints, and plantar skin under the metatarsal heads [29].

Ordinarily, the third common digital nerve, deriving from the medial plantar nerve, receives a communicating bough from the lateral plantar nerve, which passes deep to the transverse metatarsal ligament at the third IMS, which is the narrowest space, and being for this reason less mobile during weightbearing, it is explained why this is a common location for the syndrome [30]. Women are usually affected much more than men, lending credence to the presupposition that footwear is a contributing factor in the aetiology of this disorder [4].

Nowadays, four etiopathogenetic theories have been proposed [31]: chronic traction damage [30], inflammatory environment due to intermetatarsal bursitis [32], compression by the deep transverse intermetatarsal ligament [33] and ischemia of vasa nervorum [34].

Nevertheless, some of these biomechanical convictions have been denied over the years. The belief that CMS would more commonly occur in the third interspace in a more pronated foot, because of hypermobility of the lateral column relative to the medial column, is not supported anymore from the recent studies. Even the reasonable hypothesis that individuals with a high body mass index (BMI) should increase pressure in the forefoot during the propulsive phase of gait, which could traumatize plantar interspace nerves, was not confirmed by latest gait analysis outcomes. However, a strong association between the presence of CMS and a restriction of ankle dorsiflexion was demonstrated [35].

CMS diagnosis is mostly clinical and needs an accurate physical examination through various signs described in literature. Thumb index finger squeeze test and Mulder’s sign appear to have the highest sensibility and sensitivity [30,36]. In the analysed studies, Mulder’s click has been evaluated in 100% of cases, together with palpable pain (90.6%) and IMS sensory loss (67.5%). Sonographic confirmation has been the mostly used [1,14,16,27,22–24] and latest studies appears to confirm its utility, having even equal sensitivity of MRI for identification of neuroma and its size [37]. However, a negative result does not exclude the diagnosis (false negative 17%) [38].

Conservative measures such as manipulation, footwear modification, padding and injective treatments are the first therapeutic approach for the treatment of the disease and many studies evaluating their results can be found in literature [2,3,4,39]. Among these, the less invasive ones (manipulation, footwear modification and padding) are appreciated by patients but, despite of their usefulness, they cannot guarantee better results than injective treatments. Better outcomes with manipulations were reported by Govender in his RCT study [40], compared to patients

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treated with placebo. Metatarsal pad, usually molded on patient's foot, or shoes modifications showed successful effects in 32% of cases [3,4,41].

Among injections treatments, corticosteroid with or without anaesthetic is widespread utilised but even alcohol sclerosing and botulinum toxin have been used. The first is widely studied and a reduction of pain can be expected in 68–80% of cases [5,13,41–43], while the second was reported in a pilot study involving only 17 patients and showed to be of possible usefulness, opening the door to further clinical researches [39].

CI provides better results compared to shoes modification alone in 82% of patients which referred to be completely satisfied at 12 months [3]. On contrary, unsatisfactory results with CI were reported in 2 different case series [1,22], in which a complete pain relief was obtained respectively in 28% and 46% of patients. Despite these fickle results, injections may reduce significantly VAS score and improve patients' feet function [14].

This systematic review, for our knowledge, is the only one existing in the literature evaluating the reliability of CI associated or not to anesthetic. Thomson [14] favoured steroid plus anaesthetic reporting an improvement of a mean 14.1 points using the Foot Health Thermometer (FHT) scale and a significant improvement in Manchester Foot Pain and Disability Schedule walking/doing (MFPDSwd) at 3 months follow-up compared to the anaesthetic injection alone. Differently, Lizano-Diez et al. [16] stated that VAS, AOFAS and JSS do not significantly differ in patients treated with corticosteroids with or without anesthetic. A meta-analysis of these two trials [14,16] was also performed by Matthews et al. [41], affirming that the drugs combination (corticosteroid plus anaesthetic injection) seems to be more effective than anaesthetic injection alone (Weighted Mean Difference: −5.3, 95% CI: −7.5 to − 3.2). Continuous outcome measures for four of the here considered studies [17,19,26,27] showed a pre/post reduction in pain at a mean of 6.8 months (range 3 to 12) (WMD: −34.6, 95% CI: −58.1 to −11.2) [41].

Concerning the injection procedure, no differences were found at FU between free-hand and USG techniques [17,24], and no study compared different approaches.

About protocol adopted, studies reporting good results range from 1 to 3 injections but, despite this, Jain [30] suggested that 3 injections should be performed and Thomas [36] reported that multiple injection would obtain better results. However, a recent systematic review and meta-analysis on all conservative treatments [41] found that there is no evidence of better results obtained with several injections instead of a single shot and binary outcome measures with six studies [1,3,19,25–27] demonstrated success following CI at a mean of 8.4 months (range 6–12) (WSR: 34, 95% CI: 21–49%).

Free-hand or USG technique were described [3,44]: both are safe even if free-hand injection appears to give more skin complications than the USG procedure [17].

Among studies we evaluated, only 2 reported comparative results of the two techniques [2,24] and with these data no significant differences can be found between them. Approaches to the foot have been recorded from distal to proximal [1], plantar [14] and dorsal [17,20,21,23,24], but it was not possible to compare the results to indicate the best approach.

Moreover, neuroma's size could be hypothesized as a relevant factor for treatment success. Mahadevan et al. [24] asserted that neuromas with transverse diameter of more than 5 mm had worse results and Park et al. [23] declared that a big size neuroma is an important risk factor for the need of further treatments with a recurrence rate of 84% in patients with neuromas sized more than 6.3 mm.

CI are burdened by complications such as skin depigmentation and plantar fat pad atrophy [14,16,24]. Skin depigmentation was the most common complication, with a rate ranging from 5% to 18% of cases [14,17,24].

Latest studies [45] confirmed as CI remains the mainstay of conservative treatment with excellent or good satisfaction overall, and could be considered a safe intermediate treatment between simple shoe modifications and more invasive interventions. Indeed, in case of unsatisfactory results, procedures such as percutaneous alcoholization or operative options, including nerve decompression, cryogenic neuroablation or neurectomy, can always be performed.

This review has several limits. First, there is an inhomogeneity regarding the type of studies which are reported in literature on this topic and consequently a risk-of-bias assessment. The analysis is mainly based on II-IV LOE studies, the samples are non-homogenous, data are often incomplete and the follow-up is mainly at short- to mid-term. Despite this, the review could provide useful information on correct indications, management, clinical outcomes and expectations of CI in patients affected by CMS, setting the basis for further high-quality studies about this frequent foot pain condition.

5. Conclusion

This literature review analyses results in terms of pain reduction and patient satisfaction after CMS injective steroid treatment. Sonographic diagnosis is useful for instrumental confirmation, particularly to identify large neuromas. With the available data, no substantial differences were found with injections performed through dorsal, plantar or distal to proximal approaches. No difference was found using free-hand or USG techniques, although the free-hand technique seems to give more skin complications

Despite this, CI may be considered a safe intermediate treatment between shoe modifications and more invasive interventions.

Notwithstanding a good quality of the selected articles, further studies with a longer follow-up period and high quality RCTs are needed to provide more solid evidences.

Conflict of interest

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