Original Article Clinics in Orthopedic Surgery 2021;13:266-277 • https://doi.org/10.4055/cios20256

Corticosteroid Injection for Morton's Interdigital Neuroma: A Systematic Review

Jun Young Choi, MD, Hyun Il Lee, MD, Woi Hyun Hong, PhD*, Jin Soo Suh, MD, Jae Won Hur, MD

Department of Orthopedic Surgery, Inje University Ilsan Paik Hospital, Goyang,
**Medical Research Information Center, College of Medicine, Chungbuk National University, Cheongju, Korea*

Background: This review aimed to evaluate the effects of corticosteroid injections on Morton's neuroma using an algorithmic approach to assess the methodological quality of reported studies using a structured critical framework.

Methods: Several electronic databases were searched for articles published until April 2020 that evaluated the outcomes of corticosteroid injections in patients diagnosed with Morton's neuroma. Data search, extraction, analysis, and quality assessments were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and clinical outcomes were evaluated using various outcome measures.

Results: With 3–12 months of follow-up, corticosteroid injections provided satisfactory outcomes according to Johnson satisfaction scores except in two studies. Visual analog scale scores showed maximal pain reduction between 1 week and 3 months after injection. We found that 140 subjects out of 469 (29.85%) eventually underwent surgery after receiving corticosteroid injections due to persistent pain.

Conclusions: Corticosteroid injections showed a satisfactory clinical outcome in patients with Morton's interdigital neuroma although almost 30% of the included subjects eventually underwent operative treatment. Our recommendation for future research includes using more objective outcome parameters, such as foot and ankle outcome scores or foot and ankle ability measures. Moreover, studies on the safety and effectiveness of multiple injections at the same site are highly necessary.

Keywords: *Morton's neuroma, Morton's metatarsalgia, Steroid, Injection, Long term adverse effect*

Morton's interdigital neuroma was first described by Morton in 1876 as local pain under the fourth metatarsal head. It is a benign fibrous enlargement of the tissue surrounding a common plantar digital nerve, most frequently in the second and third web spaces. Diagnosis is determined based on the clinical symptoms with severe intermittent forefoot sole pain, which is aggravated by increased physical activity or constrictive footwear. Paresthesia on the affected toe can be also shown. Axial compression may be accompanied by a demonstrable painful click known as "Mulder's click." Imaging studies, including magnetic resonance imaging and ultrasound, can be useful for confirming the diagnosis or for atypical cases.

Several treatment options have been introduced from activity modification and orthosis application to open neurectomy. Before the operative treatment, radiofrequency ablation, extracorporeal shockwave therapy, cryoablation, laser therapy, or supination/pronation orthosis can be considered. A local injection therapy involves the use of corticosteroid, alcohol,[1-3] phenol,[4] botulinum toxin,[5] and capsaicin.[6] Among these, corticosteroid injection has been used most frequently as a safe and effective conservative treatment modality for patients with Morton's neuroma.

We designed this systematic review to focus on corticosteroid injection therapy for Morton's neuroma to

Received October 17, 2020; Revised December 2, 2020;
Accepted December 2, 2020
Correspondence to: Woi Hyun Hong, PhD
Medical Research Information Center, College of Medicine, Chungbuk National University, 1 Chungdae-ro, Seowon-gu, Cheongju 28644, Korea
Tel: +82-43-249-1866, Fax: +82-43-266-6775
E-mail: hong.medric@gmail.com

help readers obtain a more comprehensive understanding of this therapy. This study aimed to evaluate the positive and negative effects of corticosteroid injection on Morton's neuroma using an algorithmic approach and a structured critical framework for assessment of the methodological quality of reported studies. We addressed the current debates with the following research questions: (1) How long does the effect of corticosteroid injection persist? (2) Can we define what kind of corticosteroid is the most appropriate for Morton's neuroma (short/intermediate/long acting)? (3) Are there any differences in dorsal, plantar, or web-space approaches? (4) Are multiple injections at the same site safe and effective? (5) What is the eventual transition rate to surgery after corticosteroid injection? (6) Which types of complications are seen after corticosteroid injection for Morton's neuroma?

METHODS

Study Selection

To identify relevant studies, we used the controlled vocabulary and free texts provided in Supplementary Material 1 in an exhaustive search method to query Medline, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and Scopus databases. This study is based on the Cochrane Review Methods, and reporting was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplementary Material 2). We attempted to identify all relevant studies in English language, recording the publication type (article, poster, conference article, instructional course lecture, etc.), publication journal, and publication date. This search was updated in April 2020 and includes reference lists of included studies and any review articles that were identified. Studies designed as meta-analyses/systematic reviews, clinical randomized controlled trials (RCTs), non-randomized controlled trials (NRCTs), and controlled before-after studies (CBAs) that determined the effect of corticosteroid injection for Morton's neuroma were searched.

Eligibility Criteria

Studies were included based on the following criteria: (1) the subjects were patients who were diagnosed with Morton's neuroma and treated with corticosteroid injections and (2) the studies compared clinical outcomes for steroid treatments with conservative management with various injection approaches and assessment of positive and negative effects. Studies were excluded based on the following criteria: (1) studies that included patients who underwent operative procedures, (2) studies including patients with congenital deformities, intraoperative measures, or non-clinical outcomes, and (3) studies that did not report the effects of corticosteroid injections, including editorial comments, conference abstracts, or in vitro and animal studies.

Data Collection and Analysis

Two investigators (JYC and HIL) independently assessed the titles or abstracts of studies identified via the query and then assessed the full papers. Final inclusion was determined through discussion and consensus. The eligible data were independently abstracted into predefined formats and checked for accuracy by the investigators. We also collected information on the study characteristics: information about the authors, journal, country, publication year, sample size, subject age and sex, injected drug, number of injections, ultrasound guidance, direction of approach (dorsal, plantar, or web space), outcome parameters, and follow-up period.

The following changes related to the effects of steroid injection were extracted from the studies: (1) established objective outcome parameters, including visual analog scale (VAS), American Orthopaedic Foot and Ankle Society (AOFAS) score, EuroQol-5 dimension-3 levels (EQ-5D-3L) utility index, foot health thermometer (FHT), Manchester Oxford Foot Questionnaire (MOxFQ), Manchester Foot Pain and Disability Score (MFPDS), multidimensional affect and pain survey (MAPS), Mann scale, and Johnson satisfaction scale; (2) any other unestablished measurements to determine pain reduction or functional improvement; (3) eventual transition rate to operative treatment; and (4) complications related to steroid injection.

Studies that reported at least one of the primary objective parameters related to pain, function, or patients' satisfaction were also searched. Secondary outcomes included complications and eventual transition to operative treatment. These studies were chosen because of their association with the effects of corticosteroid injections and because a pilot search of the literature identified these as the most frequently reported and best-studied areas in Morton's neuroma treatment. We did not perform a meta-analysis due to the heterogeneity of the included studies and low statistical power since fewer than four studies were included in each field of research. Parameters to assess the outcome, timing of assessment after injection, injected agent, number with interval of injection, and approach varied widely by study.

Assessment of Methodological Quality

Two quality assessment (QA) tools based on the study designs were used to verify the quality of each retrieved article. Three reviewers (JYC, HIL, and JWH) independently assessed the methodological qualities of each study using the following QA tools: (1) A measurement tool to assess systematic reviews (AMSTAR 2[7]), (2) the Cochrane Collaboration's Risk of Bias (ROB) for RCT studies,[8] and (3) the ROB Assessment Tool for Nonrandomized Studies for NRCTs and CBAs.[9] To ensure high quality of the reviewed articles, the QA tools chosen differed depending on the study design.

Three assessors (JYC, HIL, and JWH) rated each study, reaching consensus by majority in the instance of dispute. Scoring system was as follows: 2 = yes; 1 = cannot determine, not applicable, or not reported; and 0 = no. A level of evidence (LOE) was graded as high (75%–100%), moderate (50%–75%), low (25%–50%), and very low (0%–25%). Any discrepancies were addressed by joint re-evaluation of the original article by the fourth author (JSS).

RESULTS

Identification of Studies

Fig. 1 shows a flow diagram of study selection as recommended by PRISMA.[10] In total, 11,176 studies were identified by searching four databases and manually searching relevant bibliographies as follows: 6,775 studies from Medline, 293 from Embase, 4,054 from Cochrane Library, 47 from Web of Science, and 7 by manual searching. We excluded 143 duplicate studies, plus an additional 10,981 of the remaining 11,033 studies that did not satisfy the selection criteria. We reviewed the full texts of the remaining 52 studies, which resulted in further 35 studies being excluded based on the selection criteria. The reasons for exclusion of these 35 studies were no outcome data (n = 5), insufficient information provided (n = 2), no control group (n = 25), too short follow-up period (n = 1), cadaveric study (n = 1), and glucocorticoid receptor agonist injection (n = 1). After reviewing the full texts, 17 studies were finally included in this study.[11-27]

Study Characteristics

As four studies[20,21,26,27] were systematic reviews among 17 included studies, a total of 845 participants were included in the thirteen studies. Five studies[12,16,17,23,25] with 376 participants were RCTs. Eight studies,[11,13-15,18,19,22,24] including two NRCTs[18,24] and six CBAs,[11,13-15,19,22] had 469 participants with Morton's neuroma. The characteristics of the studies, their participants, and follow-up durations are shown in Table 1. The detailed results of the QA of the four included systematic reviews are presented in Table 2.

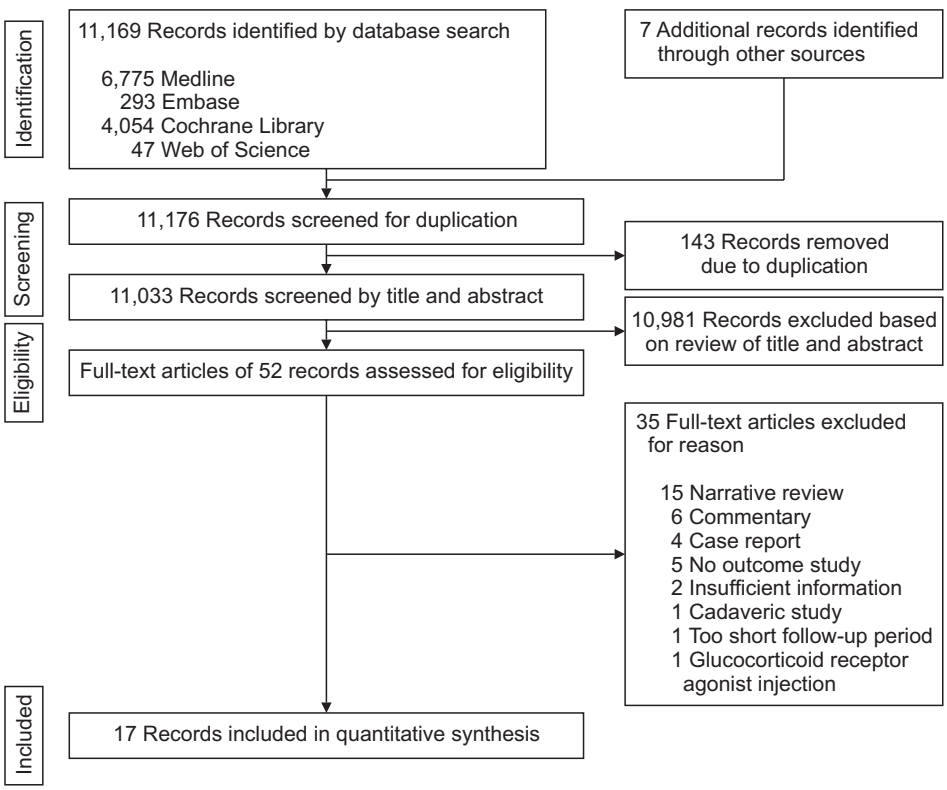

Fig. 1. A flow diagram of study selection as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Study Characteristics of 13 Studies Analyzed in This Review

Study/country	Study design	No. of participants	Age (yr)	Sex (male : female)	Follow-up duration
Ruiz Santiago et al. (2019)[23]/Spain	RCT	56 (I, 29; C, 27)	54.1 ± 2.7 (I) 50.3 ± 1.6 (C)	Not reported	6 mo
Lizano-Diez et al. (2017)[16]/Spain	RCT	35 (I ,16; C, 19)	57.7 ± 9.8 (I) 60.7 ± 11.6 (C)	4 : 12 (I) 2 : 17 (C)	6 mo
Mahadevan et al. (2016)[17]/UK	RCT	45 (I, 23; C, 22)	57.1 ± 11.7 (I) 58.6 ± 14.3 (C)	Not reported	12 mo
Edwards et al. (2015)[12]/UK	RCT	109 (I, 54; C, 55)	54.3 ± 12.2 (I) 52.6 ± 12.3 (C)	10 : 44 (I) 9 : 46 (C)	3 mo
Thomson et al. (2013)[25]/Scotland	RCT	131 (I, 64; C, 67)	53	20 : 111	12 mo
Makki et al. (2012)[18]/UK	NRCT	39; G1: 17 (neuroma diameter ≤ 5 mm), G2: 22 (neuroma diameter > 5 mm)	30 ± 7.5 (G1) 33 ± 8.4 (G2)	7 : 10 (G1) 8 : 14 (G2)	12 mo
Saygi et al. (2005)[24]/UK	NRCT	69; G1: 35 (custom fitted shoe insert), G2: 34 (steroid injection)	51.97 ± 11.8 (G1) 51.88 ± 10.97 (G2)	4 : 31 (G1) 5 : 29 (G2)	12 mo
Grice et al. (2017)[14]/UK	CBA	67	Not reported	Not reported	≥ 2 yr
Markovic et al. (2008)[19]/Australia	CBA	35	54 (29–77)	7 : 28	9 mo
Hassouna et al. (2007)[15]/UK	CBA	39	55.8 ± 13.4	7 : 32	11.4 mo
Rasmussen et al. (1996)[22]/USA	CBA	43 (51 feet)	53 (24–77)	14 : 29	4 yr (2–6)
Bennett et al. (1995)[11]/USA	CBA	115	48 (17–79)	16 : 99	3 mo
Greenfield et al. (1984)[13]/USA	CBA	62	58 (19–83)	Female, 78%	3.8 yr

Values are presented as mean ± standard deviation or mean (range).
RCT: randomized controlled trial, I: intervention, C: control, NRCT: non-randomized controlled trial, G1: group 1, G2: group 2, CBA: controlled before-after study.

A recent systematic review[20] showed high LOE scoring 27 out of 32, while the other three showed low scores (13/32,[21] 12/32[26] and 11/32[27]). Supplementary Material 3 shows the ROB graph for RCTs (Supplementary Material 3A and B) and NRCTs and CBAs (Supplementary Material 3C and D). Among RCTs, three studies[16,17,25] showed a high LOE while the other two were moderate[12] and very low.[23] Of two NRCTs, one study[18] showed moderate LOE, while the other[24] showed very low. Only two[15,19] of six CBA studies showed moderate LOE, while another two showed low LOE[14,22] and the other two showed very low LOE.[11,13]

Diversity of Outcome Measurement Timing

Fig. 2 shows the timing of parameter measurement performed in all included studies. As the locally injected steroid is known to show the effect within a month and persist for 3 to 6 months, our principle for minimal follow-up should be at least 3 months. Although the timing of outcome measurement greatly varied by authors, all included articles were fitted to this minimal follow-up cutoff (Table 1).

Diversity of Outcome Parameters

Numerous parameters were used to assess the effect of steroid injection for Morton's neuroma (VAS, AOFAS score, EQ-5D-3L utility index, FHT, MOxFQ, MFPDS, MAPS, Mann scale, and Johnson satisfaction scale). Table 3 shows the parameters used in each study. Among them, Johnson satisfaction scale[11,15-19,22] and VAS[16-18,23,25] were the two most commonly used parameters.

The Johnson satisfaction scale, which contains four subjective categories—completely satisfied, satisfied with minor reservations, satisfied with major reservations, and dissatisfied—can be easy to investigate but hard to quantify, while VAS is one of the most objective quantification methods. The summary of Johnson satisfaction scores in concerned studies is introduced in Table 4. With 3 to 12 months of follow-up, steroid injection seemed to provide satisfactory outcomes except in studies.[15,22] However, VAS (Fig. 3) showed the maximal pain reduction had appeared within 1 week to 3 months.[16-18,23] Afterwards, VAS increased again by 6 months. After 6 months, 2 studies reported that VAS decreased again by 12 months.[17,25] A

Table 2. Result of Quality Assessment of Included Systematic Reviews with a Measurement Tool to Assess Systematic Reviews (AMSTAR 2)

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16
Thomson et al. (2019)[27]	No	Partial yes	Yes	No	No	No	No	Yes	RCT, yes; NRSI, yes	No	No meta-analysis conducted	No meta-analysis conducted	No	Yes	No meta-analysis conducted	Yes
Matthews et al. (2019)[20]	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	RCT, yes; NRSI, yes	No	RCT, yes NRSI, yes	Yes	Yes	Yes	Yes	Yes
Valisena et al. (2018)[26]	No	Partial yes	Yes	No	No	Yes	No	Partial yes	RCT, yes; NRSI, yes	No	No meta-analysis conducted	No meta-analysis conducted	No	Yes	No meta-analysis conducted	Yes
Morgan et al. (2014)[21]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	No	RCT, includes only NRSI; NRSI, yes	No	No meta-analysis conducted	No meta-analysis conducted	No	No	No meta-analysis conducted	Yes

The three assessors rated each study, reaching consensus by majority in the instance of dispute.
Q: question, RCT: randomized controlled trial, NRSI: non-randomized study of healthcare interventions.

summary of detailed means with standard deviations is presented in Supplementary Material 4. We sent an e-mail to two corresponding authors[17,22] to request missing means and standard deviations and we received a response from one author.[17]

The AOFAS score,[16,18] the EQ-5D-3L utility index,[12,25] FHT,[12,25] and MFPDS[23,25] were used in only two studies each, so we decided not to summarize these results in this systematic review.

Choice of Optimal Steroid Injection

Three kinds of steroid were used in the literature (Table 3): methylprednisolone,[12,14,18,24,25] triamcinolone,[11,15,16,17,23] and betamethasone.[19,22] Multiple drugs were used in one study.[13] Methylprednisolone and triamcinolone are intermediate acting agents with a half-life of 12–46 hours. Betamethasone is a long acting agent with a longer half-life (36–72 hours). Most of the included studies used intermediate acting steroids, while only two CBA studies used a long acting agent. A further study is necessary to compare the effects of short/intermediate/long acting steroid injections.

Which Approach Is Better? Dorsal, Plantar, or Web Space Approach?

We found no comparison studies that focused on the approach site. Moreover, most of the studies did not mention which approach they used.[11-15,24] Among the rest of studies, a dorsal approach was used most commonly in four studies,[16,17,22,23] while a plantar[25] or web space[18,19] approach was used in a few studies (Table 5). Although it was not possible to determine the best approach, we could conclude that it would depend on the surgeon's preference since all approaches reported good results.

Number of Injections

Evaluation after a single injection was performed in 8 studies,[11,12,15,17-19,22,25] while the other 4 studies[13,16,23,24] evaluated multiple injections (Table 5). There was one study that did not define the number of injections.[14] Regarding multiple steroid injections, indications and timings differed greatly from one study to another, so it was not possible to determine the safety and effectiveness of multiple injections for Morton's neuroma with this level of heterogeneity.

Eventual Transition to Surgery after Steroid Injection

Table 5 includes 10 studies reporting the eventual transition rates or patient numbers after corticosteroid injection.[11,13-19,22,25] Operative procedures varied from interdigital neurectomy to nerve transposition superior to the

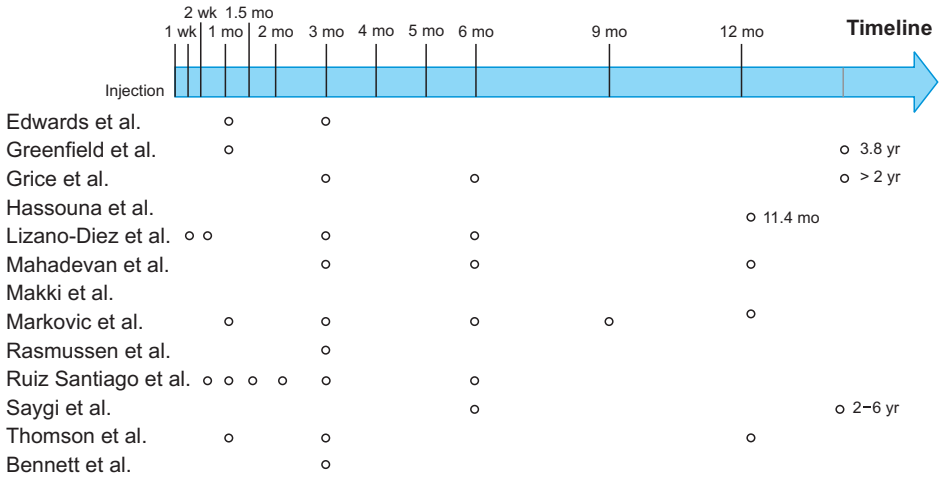

Fig. 2. The timing of parameter measurements in all included studies.

Table 3. Injected Agents and Outcome Parameters of Each Study

Study/study design	Injected agent	Outcome parameter
Ruiz Santiago et al.[23]/RCT	Triamcinolone 40 mg + 2% mepivacaine 1 mL (I, C)	VAS, MFPDS, own subjective satisfaction questionnaire
Lizano-Diez et al.[16]/RCT	Triamcinolone 40 mg + 2% mepivacaine 1 mL (I); 2% mepivacaine 2 mL (C)	VAS, AOFAS score, Johnson satisfaction scale
Mahadevan et al.[17]/RCT	Triamcinolone 40 mg + 1% lignocaine 2 mL (I, C)	VAS, MOxFQ index, Johnson satisfaction scale
Edwards et al.[12]/RCT	Methylprednisolone 40 mg + 2% lignocaine 1 mL (I); 1% lignocaine 2 mL (C)	FHT score, EQ-5D-3L utility index
Thomson et al.[25]/RCT	Methylprednisolone 40 mg + 1% lignocaine 1 mL (I); 1% lignocaine 2 mL (C)	VAS, MFPDS, FHT score, MAPS, general health thermometer, EQ-5D
Makki et al.[18]/NRCT	Methylprednisolone 40 mg + 1% lidocaine 1 mL (G1, G2)	VAS, AOFAS score, Johnson satisfaction scale
Saygi et al.[24]/NRCT	Methylprednisolone 40 mg + Prylocayn HCL 1 mL (G2)	Own subjective satisfaction questionnaire
Grice et al.[14]/CBA	Methylprednisolone 40 mg + 0.5% Marcaine	Existence of pain, activity level, use of orthosis
Markovic et al.[19]/CBA	Betamethasone 1 mL + 1% lidocaine 0.5 mL	Johnson satisfaction scale, modified lower extremities functional scale (functional daily activity)
Hassouna et al.[15]/CBA	Triamcinolone 20 mg + 0.5% bupivacaine 2 mL	Johnson satisfaction scale, subjective pain intensity, subjective activity limitation, rate of foot wear modification
Rasmussen et al.[22]/CBA	Betamethasone 1 mL + 0.5% bupivacaine 1 mL	Johnson satisfaction scale, subjective pain intensity, subjective activity limitation, rate of foot wear requirement, Mann scales
Bennett et al.[11]/CBA	Triamcinolone 40 mg + Xylocaine 2 mL	Johnson satisfaction scale
Greenfield et al.[13]/CBA	Prednisolone tebutate 1 mL or Betamethasone 1 mL or triamcinolone 1 mL + 1% xylocaine 2 mL	Time to pain relief (short-term effect), subjective degree of pain relief (long-term effect)

RCT: randomized controlled trial, I: intervention, C: control, VAS: visual analog scale, MFPDS: Manchester foot pain and disability score, AOFAS: American Orthopaedic Foot and Ankle Society, MOxFQ: Manchester Oxford foot questionnaire, FHT: foot health thermometer, EQ-5D-3L: EuroQol-5 dimension-3 levels, MAPS: multidimensional affect and pain survey, NRCT: non-randomized controlled trial, G1: group 1, G2: group 2, CBA: controlled before-after study.

intermetatarsal ligament. In our study, we found that 140 subjects out of 469 (29.85%) eventually underwent operative treatment after steroid injection due to the persistent pain.

Complications Related to Steroid Injection

Table 5 shows the possible complications related to corticosteroid injection in all included studies. Skin depigmentation on the injected site was mentioned in six stud-

Table 4. Johnson Satisfaction Scores of All Included Studies

Study/study design	Completely satisfied	Satisfied with minor reservations	Satisfied with major reservations	Dissatisfied
Lizano-Diez et al.[16]*/RCT	6/16 (37.5)	4/16 (25)	3/16 (18.75)	3/16 (18.75)
Mahadevan et al.[17]†/RCT	7/23 (30.5)	9/23 (39)	1/23 (4.5)	6/23 (26)
Makki et al.[18]*/NRCT	17/39 (44))	9/39 (23)	7/39 (18)	6/39 (15)
Hassouna et al.[15]‡/CBA	12/39 (31)	6/39 (15)	5/39 (13)	16/39 (41)
Markovic et al.[19]§/CBA	15/39 (38)	11/39 (28)	Not mentioned	Not mentioned
Rasmussen et al.[22]‖/CBA	3/51 (6)	3/51 (6)	9/51 (18)	36/51 (71)
Bennett et al.[11]†/CBA	27/58 (47%) → Improved, 31/58 (53%) → not improved (no detailed information)			

Values are presented as number (%). The data from Makki et al.[18] was the sum of all neuroma regardless of size.
RCT: randomized controlled trial, NRCT: non-randomized controlled trial, CBA: controlled before-after study.
Outcomes were measured at †3, *6, §9, ‡12, or ‖48 months after the injection.

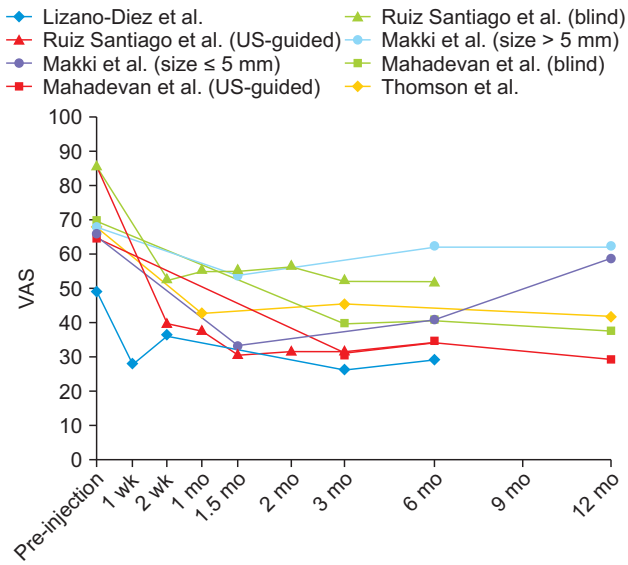

Fig. 3. The effect of pain relief using a visual analog scale (VAS) after corticosteroid injection.

ies[16-19,23,25] with a total rate of 3.40% (10/294 patients). Skin atrophy was mentioned in two studies (5.88%, 3/51),[16,19] while fat pad atrophy was mentioned in five studies,[16-19,25] with a rate of 0.93% (2/216). No major complications, such as hyperglycemia, infection, or tendon rupture were reported. Interestingly, we found no studies reporting post-injection flare or facial flushing, which are often reported as complications after local steroid injection.

DISCUSSION

Our data are meaningful because this review on corticosteroid injections for Morton's interdigital neuroma included the largest number of studies to date. Fig. 4 shows summary answers to the research questions posed in the introduction. While we were screening the studies, we found 5 remarkable systematic reviews on conservative treatment for Morton's neuroma.[20,21,26-28] A Cochrane review in 2004[28] only reported the effects of supinatory or pronatory insoles among several conservative treatment options. In that review, they concluded that there was no evidence to support the use of supinatory insoles. They also reported that there were no RCTs reporting the effect of corticosteroid injections. Since then, a number of clinical trials have been published with a few outstanding RCTs.[16,17,25] With these, a systematic review by Valisena et al.[26] reported a 51% success rate for corticosteroid injections. However, it is still problematic that they only included two studies, including one NRCT[18] and one CBA.[19]

Two recent systematic reviews,[20,27] which revealed the effectiveness of all kinds of nonoperative interventions, included seven[15-17,19,24,25,29] and five[17-19,24,25] studies on corticosteroid injections. Matthews et al.[20] measured the binary outcomes with six studies[15-17,19,24,29] demonstrating success following corticosteroid injection after a mean period of 8.4 months. These two recent systematic reviews contained various conservative modalities, such that it was very difficult to ascertain the advantages and disadvantages of corticosteroid injections. At that point, we decided to create an evidence map focused on corticosteroid injections. To facilitate this, we searched for answers to certain clinical questions, which every clinician might have wondered while they were treating patients with Morton's neuroma. Compared to the two recent systematic reviews, we included the largest number of studies with two new RCTs[12,23] and four new CBAs.[11,13,14,22] Fig. 5 shows the

Table 5. Approach, Number of Injection, Ultrasound Guidance, Eventual Transition Number (Rate) to Operation after Complications Related to Steroid Injections and Corticosteroid Injections

Study/study design	Approach	No. of injections	Ultrasound guidance	Eventual transition to surgery after steroid injection	Related complication
Ruiz Santiago et al.[23]/RCT	Dorsal (I, C)	Maximum 4 injections in 3 months if the symptom persisted: 2.1 ± 0.2 times (I), 2.7 ± 0.1 times (C)	Ultrasound guided (I); blind (C)	Not investigated	Skin depigmentation (I: 1/29, C: 5/27); local hypersensitivity (I: 1/29, C: none); crossover toe (I: 1/29, C: none)
Lizano-Diez et al.[16]/RCT	Dorsal (I, C)	Three injections at 1 week (I, C)	Blind (I, C)	I: 7/16 (43.8%), C: 10/19 (52.6%)	Skin atrophy (I: 3/16, C: 0/19); no skin depigmentation; no fat pad atrophy
Mahadevan et al.[17]/RCT	Dorsal (I, C)	Once (I, C)	Ultrasound guided (I); blind (C)	I: 14/23 (60.9%), C: not investigated	Skin depigmentation (I: none, C: 1/22); no fat pad atrophy
Edwards et al.[12]/RCT	Not reported	Once (I, C)	Ultrasound guided (I, C)	Not investigated	Not reported
Thomson et al.[25]/RCT	Plantar (I,C)	Once (I, C)	Ultrasound guided (I, C)	I: 19/60 (31.7%), C: 28/65 (43.1%)	Skin depigmentation (I: 3/60, C: 1/65); plantar fat pad atrophy (I: 2/60, C: 0/19)
Makki et al.[18]/NRCT	Web space	Once (G1, G2)	Ultrasound guided	G1: 2/17 (11.8%), G2: 28/65 (43.1%)	No fat pad atrophy; no skin depigmentation
Saygi et al.[24]/NRCT	Not reported	Double injections at 3 week (G2)	Not reported	Not investigated	Not reported
Grice et al.[14]/CBA	Not reported	Repeated injection in 11 patients (16%); number not reported	Not reported	19/67 (28.4%)	Not reported
Markovic et al.[19]/CBA	Web space	Once	Ultrasound guided	12/35 (34.3%)	No skin depigmentation; no fat pad atrophy; no skin atrophy; no steroid flare; no anaphylaxis
Hassouna et al.[15]/CBA	Not reported	Once	Ultrasound guided	3/39 (7.7%)	Not reported
Rasmussen et al.[22]/CBA	Dorsal	Once	Blind	24/51 (47.1%)	Not reported
Bennett et al.[11]/CBA	Not reported	Once	Not reported	24/115 (20.9%)	Not reported
Greenfield et al.[13]/CBA	Not reported	Repeated injection at 1 to 3 week if the symptom persisted; mean, 3.07 times	Blind	11/62 (17.7%)	Not reported

RCT: randomized controlled trial, I: intervention, C: control, NRCT: non-randomized controlled trial, G1: group 1, G2: group 2, CBA: controlled before-after study.

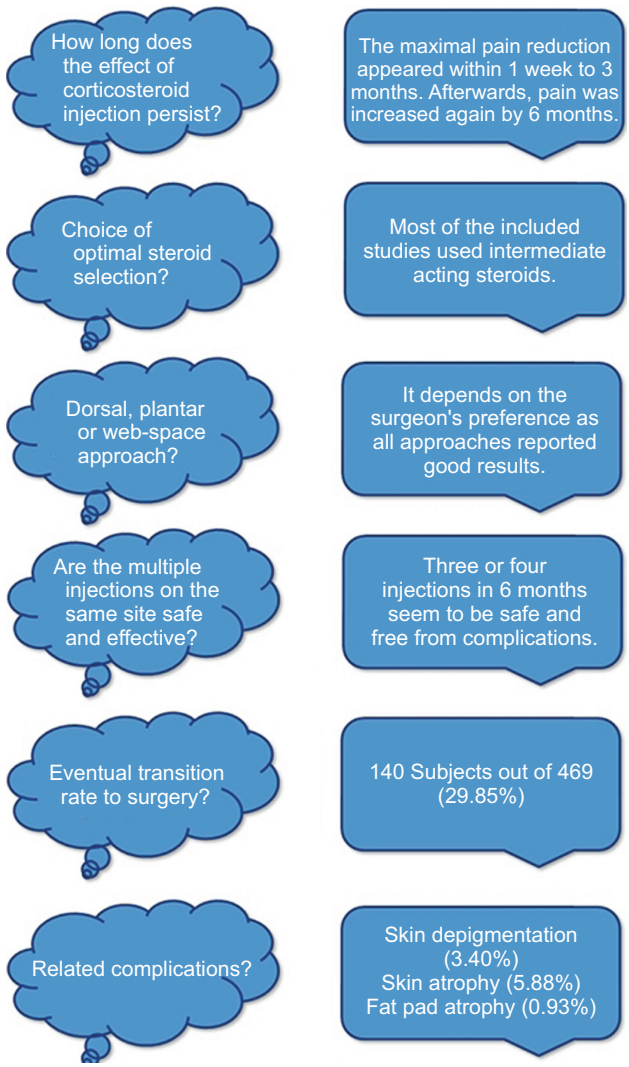

Fig. 4. Summary of answers to the research questions posed in the introduction.

comparison of the number of studies included in previous systematic reviews and our study.

Originally, we planned to include a question about the necessity of ultrasound in corticosteroid injection. However, we finally decided not to show our results as the previous systematic reviews had already reported results similar to ours. A systematic review by Morgan et al.[21] focused on the use of ultrasound during therapeutic injections to treat Morton's neuroma. Although they included only seven CBAs for corticosteroid injection, they concluded that ultrasound has a vital role. With regard to ultrasound guidance, Matthew et al.[20] reported an odds ratio of 9.5 (95% confidence interval, 1.0–82.4) compared to non-guidance in their meta-analysis. In our review, injections performed under ultrasound guidance were reported in five studies[12,15,18,19,25] while blind injections were performed in four articles.[11,13,16,22] We also found two RCTs comparing ultrasound-guided injections with blind injections.[17,23] However, we thought a meta-analysis of these studies was impossible as the characteristics of the selected studies were totally heterogeneous with regard to the injected agent, outcome parameters, outcome measurement timing, number of injections, and follow-up period. With current data, we recommend the use of ultrasound depending on the surgeon's experience and confidence. Ultrasound guidance may not be necessary if the surgeon can ensure solid and constant results with blind injection. Nevertheless, ultrasound-guided injection seems to not have any harmful effects at least.

It is very disappointing that we could not determine the optimal agent with regard to the duration of action. We generally believe that long acting agents would result in better clinical outcomes. However, we should not forget that these long acting agents could have higher complica-

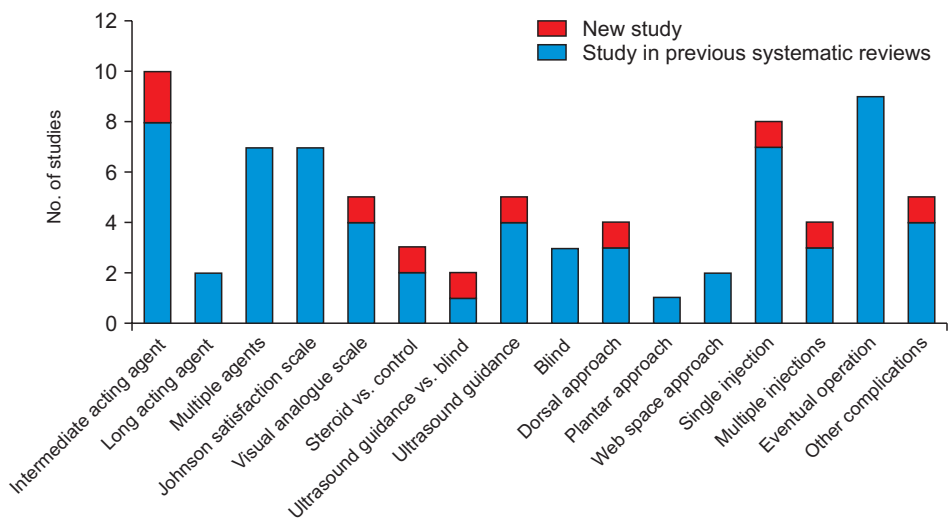

Fig. 5. Comparison of the number of included studies in previous systematic reviews and our study.

tion rates. Although most of the included studies used intermediate acting agents, we suggest that it would be very helpful if future studies focus on the comparison of positive and negative outcomes of various injected agents. Similarly, we could not determine the optimal approach for corticosteroid injections. However, we believe that this would depend on the surgeon's preference since all approaches were associated with good results.

Regarding the number of injections, four studies[13,16,23,24] showed the results following multiple corticosteroid injections. As the number of injections and duration of treatment varied greatly from study to study (maximum four injections in 3 months if the symptoms persisted,[23] three injections in a week,[16] two injections every 3 weeks,[24] and repeated injections every 1 to 3 weeks[13]), it was very difficult to determine the optimal number of injections and duration of treatment. However, in our opinion, three or four injections over a period of 6 months seem to be safe and obviate unwanted complications.

As the previous systematic reviews have already focused on the positive effects of corticosteroid injection, we specifically tried to reveal the negative side effects in this review. Therefore, it was meaningful that we could answer the question about the eventual transition rate to surgery after corticosteroid injection (29.85%). Many included studies mentioned transition rates or numbers, although the procedures varied from study to study.[11,13-19,22,25] In most studies, the preferred operative procedure was affected interdigital neurectomy, for which the operative outcomes were good. With regard to related complications, we concluded that corticosteroid injection was a safe treatment option as no studies reported any major systematic complications that could be caused by corticosteroid injection (hyperglycemia, infection, or tendon rupture). On the contrary, we suspect that the complications were not fully reported because even the relatively common complications (post-injection flare or facial flushing) were not mentioned.

Future research should include studies that compare different agents and different injection intervals, focusing on the side effects or eventual transition rate to surgery. To achieve more objective results, outcome parameters, such as foot and ankle outcome scores or foot and ankle ability measures,[30] will be greatly helpful. In addition, we strongly suggest a monthly outcome evaluation after injections to determine the onset and cessation of the positive effects. Moreover, studies about the safety and effectiveness of multiple injections at the same site are highly necessary.

As with any research, this systematic review had some limitations. While the systematic search of the literature identified a modest body of evidence, there were concerns with the methodological quality. The areas of concern included the sample sizes and sampling techniques, the diagnostic criteria, the development and administration of intervention and its parameters, and the lack of psychometrically robust outcome measures. Given that almost half of the included studies were CBAs, the generalizability of the findings of these studies was limited. Because of the diversity of the outcome measures used and the heterogeneity of the interventions, a direct comparison of results between the studies was not possible.

In conclusion, with 3 to 12 months of follow-up, corticosteroid injections provided satisfactory outcomes based on Johnson satisfaction scores. VAS showed that maximal pain reduction appeared at 1 week to 3 months. After 3 months, the effect seemed to be terminated as VAS increased again by 6 months. Regarding multiple steroid injections, three or four injections over 6 months seems to be safe and avoids unwanted complications, although there was a lack of good quality studies about multiple injections. Almost 30% of included subjects eventually underwent operative treatment after steroid injection. Skin depigmentation and skin or fat pat atrophy were reported as minor complications. However, we could not determine the optimal agent or the best approach site for corticosteroid injections.

Future research should include studies that compare different agents and different injection intervals, focusing on the side effects or eventual transition rate to surgery. To achieve more objective results, outcome parameters, such as foot and ankle outcome scores or foot and ankle ability measures,[30] will be greatly helpful. In addition, we strongly suggest a monthly outcome evaluation after injections to determine the onset and cessation of the positive effects. Moreover, studies about the safety and effectiveness of multiple injections at the same site are highly necessary.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This research was supported by a grant from the Medical Research Information Center (MedRIC) of the National Research Foundation through the Ministry of Science and ICT (2018R1A6A6040880), Korea.

SUPPLEMENTARY MATERIAL

Supplementary material is available in the electronic version of this paper at the CiOS website, www.ecios.org.

ORCID

Jun Young Choi https://orcid.org/0000-0002-3864-9521
Hyun Il Lee https://orcid.org/0000-0002-0957-0988
Woi Hyun Hong https://orcid.org/0000-0002-1212-4444
Jin Soo Suh https://orcid.org/0000-0002-6830-9149
Jae Won Hur https://orcid.org/0000-0002-5527-8005

REFERENCES

1. Espinosa N, Seybold JD, Jankauskas L, Erschbamer M. Alcohol sclerosing therapy is not an effective treatment for interdigital neuroma. Foot Ankle Int. 2011;32(6):576-80.
2. Gurdezi S, White T, Ramesh P. Alcohol injection for Morton's neuroma: a five-year follow-up. Foot Ankle Int. 2013;34(8):1064-7.
3. Pasquali C, Vulcano E, Novario R, Varotto D, Montoli C, Volpe A. Ultrasound-guided alcohol injection for Morton's neuroma. Foot Ankle Int. 2015;36(1):55-9.
4. Magnan B, Marangon A, Frigo A, Bartolozzi P. Local phenol injection in the treatment of interdigital neuritis of the foot (Morton's neuroma). Chir Organi Mov. 2005;90(4):371-7.
5. Climent JM, Mondejar-Gomez F, Rodriguez-Ruiz C, Diaz-Llopis I, Gomez-Gallego D, Martin-Medina P. Treatment of Morton neuroma with botulinum toxin A: a pilot study. Clin Drug Investig. 2013;33(7):497-503.
6. Campbell CM, Diamond E, Schmidt WK, et al. A randomized, double-blind, placebo-controlled trial of injected capsaicin for pain in Morton's neuroma. Pain. 2016;157(6):1297-304.
7. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
8. Higgins JP, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions version 6.1 [Internet]. Chichester, UK: John Wiley & Sons; 2019 [cited 2021 Jan 15]. Available from: https://training.cochrane.org/handbook/current.
9. Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. J Clin Epidemiol. 2013;66(4):408-14.
10. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
11. Bennett GL, Graham CE, Mauldin DM. Morton's interdigital neuroma: a comprehensive treatment protocol. Foot Ankle Int. 1995;16(12):760-3.
12. Edwards RT, Yeo ST, Russell D, et al. Cost-effectiveness of steroid (methylprednisolone) injections versus anaesthetic alone for the treatment of Morton's neuroma: economic evaluation alongside a randomised controlled trial (MortISE trial). J Foot Ankle Res. 2015;8:6.
13. Greenfield J, Rea J Jr, Ilfeld FW. Morton's interdigital neuroma. Indications for treatment by local injections versus surgery. Clin Orthop Relat Res. 1984;(185):142-4.
14. Grice J, Marsland D, Smith G, Calder J. Efficacy of foot and ankle corticosteroid injections. Foot Ankle Int. 2017;38(1):8-13.
15. Hassouna H, Singh D, Taylor H, Johnson S. Ultrasound guided steroid injection in the treatment of interdigital neuralgia. Acta Orthop Belg. 2007;73(2):224-9.
16. Lizano-Diez X, Gines-Cespedosa A, Alentorn-Geli E, et al. Corticosteroid injection for the treatment of Morton's neuroma: a prospective, double-blinded, randomized, placebo-controlled trial. Foot Ankle Int. 2017;38(9):944-51.
17. Mahadevan D, Attwal M, Bhatt R, Bhatia M. Corticosteroid injection for Morton's neuroma with or without ultrasound guidance: a randomised controlled trial. Bone Joint J. 2016;98(4):498-503.
18. Makki D, Haddad BZ, Mahmood Z, Shahid MS, Pathak S, Garnham I. Efficacy of corticosteroid injection versus size of plantar interdigital neuroma. Foot Ankle Int. 2012;33(9):722-6.
19. Markovic M, Crichton K, Read JW, Lam P, Slater HK. Effectiveness of ultrasound-guided corticosteroid injection in the treatment of Morton's neuroma. Foot Ankle Int. 2008;29(5):483-7.
20. Matthews BG, Hurn SE, Harding MP, Henry RA, Ware RS. The effectiveness of non-surgical interventions for common plantar digital compressive neuropathy (Morton's neuroma): a systematic review and meta-analysis. J Foot Ankle Res. 2019;12:12.
21. Morgan P, Monaghan W, Richards S. A systematic review of

ultrasound-guided and non-ultrasound-guided therapeutic injections to treat Morton's neuroma. J Am Podiatr Med Assoc. 2014;104(4):337-48.

22. Rasmussen MR, Kitaoka HB, Patzer GL. Nonoperative treatment of plantar interdigital neuroma with a single corticosteroid injection. Clin Orthop Relat Res. 1996;(326):188-93.
23. Ruiz Santiago F, Prados Olleta N, Tomas Munoz P, Guzman Alvarez L, Martinez A. Short term comparison between blind and ultrasound guided injection in morton neuroma. Eur Radiol. 2019;29(2):620-7.
24. Saygi B, Yildirim Y, Saygi EK, Kara H, Esemenli T. Morton neuroma: comparative results of two conservative methods. Foot Ankle Int. 2005;26(7):556-9.
25. Thomson CE, Beggs I, Martin DJ, et al. Methylprednisolone injections for the treatment of Morton neuroma: a patient-blinded randomized trial. J Bone Joint Surg Am. 2013;95(9):790-8.
26. Valisena S, Petri GJ, Ferrero A. Treatment of Morton's neuroma: a systematic review. Foot Ankle Surg. 2018;24(4):271-81.
27. Thomson L, Aujla RS, Divall P, Bhatia M. Non-surgical treatments for Morton's neuroma: a systematic review. Foot Ankle Surg. 2020;26(7):736-43.
28. Thomson CE, Gibson JN, Martin D. Interventions for the treatment of Morton's neuroma. Cochrane Database Syst Rev. 2004;(3):CD003118.
29. Park YH, Lee JW, Choi GW, Kim HJ. Risk factors and the associated cutoff values for failure of corticosteroid injection in treatment of Morton's neuroma. Int Orthop. 2018;42(2):323-9.
30. Martin RL, Irrgang JJ, Burdett RG, Conti SF, Van Swearingen JM. Evidence of validity for the Foot and Ankle Ability Measure (FAAM). Foot Ankle Int. 2005;26(11):968-83.