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REVIEW ARTICLE (META-ANALYSIS)

Clinical Efficacy of Botulinum Toxin in the Treatment of Plantar Fasciitis: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Objective: To evaluate the efficacy of botulinum toxin A (BTX-A) for the treatment of plantar fasciitis through a meta-analysis of randomized controlled trials (RCTs) focusing on pain and functional outcomes since current literature has supported a potential benefit of BTX-A.

Data Sources: The MEDLINE, EMBASE, Web of Science, and Scopus databases were searched until December 2020 for RCTs reporting the effects of BTX-A injections on plantar fasciitis. The complementary literature search included Cochrane Central Register of Controlled Trials, Clinicaltrials.gov, and greylit.org.

Study Selection: Only RCTs assessing the effect of BTX-A injections on pain, functional improvement, or plantar fascia thickness in patients with plantar fasciitis were included. Multiple researchers carried out the screening process of the 413 records.

Data extraction: Data were extracted independently and in duplicate using a standardized data extraction format. Information was contrasted by a third observer.

Data Synthesis: BTX-A injections resulted in significant pain relief (mean difference, −2.07 [95% CI, −3.21 to −0.93]; P=.0004; I^2=97%) and functional improvement (standardized mean difference, 1.15 [95% CI, 0.39-1.91]; P=.003; I^2=87%). A subanalysis indicated that pain relief was sustained at 12 months while functional improvement remained significant after 0-6 months. The results were not affected by a single study after sensitivity analysis. The site of injection and the use or not of ultrasound-guided injections may account for potential sources of interstudy heterogeneity.

Conclusions: This meta-analysis suggests both a statistically significant and a clinically meaningful improvement on plantar fasciitis symptoms after BTX-A treatment.

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Plantar fasciitis is a common injury that occurs in the plantar aponeurosis as a result of constant microtrauma and excessive strain.[1,2] This affection is the most frequent cause of plantar heel pain, which is estimated to occur in approximately 10% of the general population,[3-5] where active working adults between the ages of 25 and 65 years account for 83% of these patients.[2] The highest risk of occurrence is reported between 40 and 60 years of age, regardless of sex.[6] Obesity, prolonged standing, excessive foot pronation, running, and decreased ankle dorsiflexion are the main predisposing factors for plantar fasciitis.[7,8]

This condition is essentially a chronic degenerative process owing to the repetitive stress and weight-bearing–associated microtears. The tissue granulation, collagen disarrange, lack of

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traditional inflammation, and thickening and heterogeneity of the plantar fascia suggest a noninflammatory process with vascular dysfunction.[2] The diagnosis of plantar fasciitis is primarily based on the clinical history and physical examination. Image studies are rarely required, although ultrasonography examination may evidence thickening and swelling of the plantar fascia, a typical characteristic of plantar fasciitis.[2,9]

Because plantar fasciitis is characterized by a multifactorial etiology, multiple therapeutic options have been tested.[10] The different treatment modalities may be classified into noninvasive and invasive therapies, including plantar fascia stretching exercises, taping, shoe inserts, night splints, nonsteroidal anti-inflammatory drugs, extracorporeal shock wave therapy, corticosteroid injections, platelet-rich plasma injections, botulinum toxin injections, and surgical approaches.[3,9,11] Noninvasive interventions have usually been the first treatment option (used in 85%-90% of cases) for treating plantar fasciitis,[5] with an effectiveness of up to 90%.[1] A recent meta-analysis reported inconclusive results for clinical practice of both conservative and nonpharmacologic treatments regarding pain relief in patients with plantar heel pain.[12] Thus, injected therapies are frequently used in patients who did not respond to noninvasive treatments.

Previous evidence suggesting the potential benefit of botulinum toxin A (BTX-A) in the treatment of chronic pain and musculoskeletal injuries has led to the development of randomized controlled trials (RCTs) evaluating the use of BTX-A in plantar fasciitis. Most of these trials have reported positive effects of BTX-A for pain relief and functional improvement in the short-[13-15] and medium-term,[16] while others studies have shown conflicting results.[17,18] A previous network meta-analysis has revealed that the BTX-A treatment for plantar fasciitis induces pain reduction in the short-term.[19] However, data from clinical trials investigating the long-term effect of BTX-A are now being reported.[20,21]

Given that there are recent RCTs that were not included in the previous meta-analysis, we decided to evaluate the efficacy of BTX-A for the treatment of plantar fasciitis including both the short- and long-term effect.

Methods

This systematic review was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[22] The execution was guided by a registered protocol in a publicly accessible database (PROSPERO registration no.: CRD42020213090).

Eligibility criteria

Our meta-analysis only included RCTs (parallel, crossover, or pre-post treatment) assessing the effect of BTX-A injections on either pain (visual analog scale [VAS]), functional improvement (Maryland Foot Score, Foot Health Status Questionnaire [FHSQ], Foot and Ankle Disability Index, Foot and Ankle Ability Measures, American Orthopedic Foot and Ankle Society score), or plantar fascia thickness in patients with plantar fasciitis. We considered studies enrolling patients with a clinically or image-based diagnosis of chronic plantar fasciitis, in which plantar fasciitis is defined as pain at the plantar medial aspect of the heel, tenderness at the plantar aspect of the medial calcaneal tuberosity around the fascia insertion, and the presence of "start-up pain" (on first walking in the morning and after a period of rest that gets better after walking for a while).[23] There was no language restriction. Studies were excluded if they had relevant missing data for statistical analysis or did not fulfill the study design (cohorts, case-control studies, cross-sectional studies).

List of abbreviations:

BTX-A	**botulinum toxin A**
FHSQ	**Foot Health Status Questionnaire**
MD	**mean difference**
MCID	**minimal clinically important difference**
RCT	**randomized controlled trial**
VAS	**visual analog scale**

Information sources and search strategy

A combination of Medical Subjects Headings and search terms (plantar heel pain, chronic plantar fasciitis, chronic heel pain, plantar fasciopathy) were selected to find original articles or abstracts in any language. MEDLINE, Embase, Web of Science, and Scopus databases were searched from each database inception to December 2020 (supplemental appendix S1, available online only at http://www.archives-pmr.org/). We addressed the possibility of nonpublication and dissemination bias by performing a literature search in Cochrane Central Register of Controlled Trials, Clinicaltrials.gov, and greylit.org to decrease the possibility of missing a study. Where possible, a funnel plot was developed to assess this aspect.

Study selection process

Four authors, working as independent pairs, screened titles, abstracts, and full-text articles for eligibility. A pilot screening process for the title and abstracts and full-text phases was performed before formally beginning each phase. The chance-adjusted agreement was quantified using the kappa statistic.[24] Any disagreement was resolved by consensus with the remaining authors. The Distiller Systematic Review Software[a] was used for the management of the data during the aforementioned selection process.

Data collection process

Data were extracted independently and in duplicate using a standardized data extraction format. Eligible studies were reviewed, and the following data were abstracted: (1) first author's name; (2) year of publication; (3) study design; (4) target population; (5) number of participants in the intervention and control groups; (6) treatment application method; (7) age, sex, and body mass index of study participants; (8) values of the scales reporting pain or functional assessment at baseline and follow-up; and (9) plantar fascia thickness.

Risk of bias

A systematic assessment of bias in the included studies was performed using the Cochrane criteria Risk of Bias tool version 2.0.[25] The domains used for the assessment of each study were as follows: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and overall bias. The risk-of-bias judgments for each domain are "low risk of bias," "some concerns," or "high risk of bias."

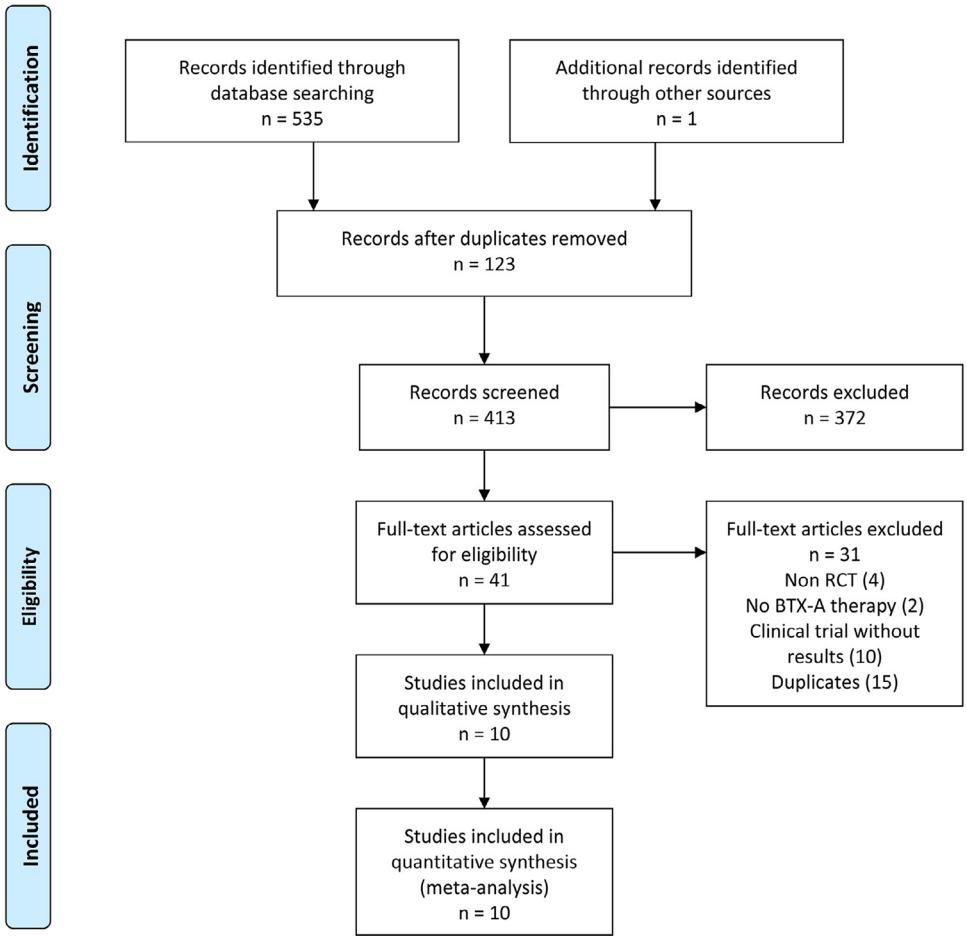

Fig 1 Flowchart of the number of studies identified and included in this meta-analysis.

Quantitative data synthesis

For each study, a summary of the intervention effect is reported in mean difference (MD) or standardized mean difference for pain, functional, and plantar fascia thickness. When the outcome measures were reported as the median and interquartile range (or 95% CI), mean and SD values were estimated with the methods described by Hozo et al[26] and Wan et al[27] If mean and 95% CI was available, the SD was estimated with the next formula: SD=sqrt(n)×[(upper limit-lower limit)/3.92], where sqrt is the square root and (n) is the number of patients in the study arm. The net change in measurements (MD) was calculated as follows: measure at end of follow-up − measure at baseline. To estimate the SD of the MD, the following formula was used: $SD=sqrt[(SD_{pretreatment})^2+(SD_{posttreatment})^2-(2R\times SD_{pretreatment}\times SD_{posttreatment})]$, assuming a correlation coefficient (R) of 0.5. The statistical analysis was performed using the software Review Manager V5.3.[b] To evaluate the influence of each study on the overall effect size, a sensitivity analysis was performed with the leave-one-out method. [28,29]

The exploration of consistency, specifically focusing on the heterogeneity of the studies to include was examined by applying Cochrane's Q Statistic test considering a P value of <.05 as statistically significant. Furthermore, the I^2 statistic was reported, taking into consideration a 0-25% of heterogeneity between studies as unimportant, >25-50% as moderate, and >50% as important heterogeneity. In the case of having a heterogeneity of >50% between studies we performed a random-effects model for the meta-analysis and in case of heterogeneity being <50% we performed a fixed-effects model.

As a secondary analysis, we compared our results against available established minimal clinically important difference (MCID) criteria in plantar fasciitis to assess if changes are clinically meaningful.

Publication bias

Where possible, a funnel plot was generated to assess the presence of potential publication bias for the outcomes of this meta-analysis.

Results

Study selection process

The multiple database searches identified 535 articles; an additional reference was identified by manual searching in previously published reviews. After duplicated records were removed, 413 studies were screened and 372 of them were excluded because they did not meet the inclusion criteria. Subsequently, 41 full-text articles were reviewed for possible eligibility and 31 were excluded for the following reasons: not being an RCT (4), not using BTX-A therapy (2), not having complete results (10), and duplicates (15). Finally, 10 studies fulfilled the eligibility criteria and were included in the systematic review and meta-analysis. The complete study selection process is shown in fig 1.

Table 1 Characteristics of the included studies

Author	Study Design	Target Population	Follow-up	n	Study Groups (No. of Injections)	Injected Dose (Volume)	Site of Injection	US-Guided Injection	Age (y)	Female, n (%)	BMI	Pain Score at Baseline	Functional Score at Baseline
Abbasian et al[20]	Randomized, double-blind, placebo-controlled	Chronic plantar fasciitis	12 mo	15	BTX-A	70 U (1.5 mL)	Medial head of the gastrocnemius	Yes	47.3±6.1	6 (40.0)	24.8±1.9	8.0±0.8*	45.5±5.7†
				13	Normal saline	1.5 mL			45.6±9.7	4 (30.8)	29.3±1.3	7.8±0.8*	48.4±5.8†
Ahmad et al[16]	Randomized, double-blind, placebo-controlled	Acute or chronic plantar fasciitis	12 mo	25	IBTA	100 U (1.0 mL)	Origin of the plantar fascia and tender region	Electromyographic guidance	48.6 (33-61)‡	17 (68.0)	ND	7.2 (6.0-10.0)*,‡	36.3 (25.0–43.8)‡,§
				25	Normal saline	1.0 mL			51.3 (31-69)‡	19 (76.0)	ND	8.4 (7.0-10.0)*,‡	35.9 (25.0-46.9)*,§
Babcock et al[13]	Randomized, double-blind, placebo-controlled	Chronic plantar fasciitis	8 wk	22 ft	BTX-A	70 U (0.7mL)	Origin of the plantar fascia and tender region	No	44 (21-65)‖	15 (68.2)	ND	5.1 (2.0-9.7)*,‡	44.0 (31.0-73.0)*,¶
				21 ft	Normal saline	0.7 mL				15 (71.4)	ND	4.9 (1.0-9.7)*,‡	46.0 (35.0–90.0)*,¶
Díaz-Llopis et al[15]	Randomized, single-blind, controlled	Chronic plantar fasciitis	6 mo	28	BTX-A	70 U (0.7 mL)	Origin of the plantar fascia and tender region	No	51.5±14.8	19 (67.9)	ND	29.1±19.5#	43.5±23.1**
				28	Corticosteroid	Betamethasone 6 mg/mL (2.0 mL)+mepivacaine 1% (0.5 mL)			56.4±14.7	18 (64.3)	ND	31.6±21.0#	42.2±19.7**
Elizondo-Rodríguez et al[30]	Randomized, double-blind, controlled	Heel pain at the insertion of the plantar fascia	6 mo	19	BTX-A	250 U (5.0mL)	Gastrocnemius and soleus	No	41.6 (29-53)‡	9 (47.4)	ND	7.1±1.8*	62.1±9.8¶
				17	Corticosteroid	Dexamethasone 8 mg/mL (2.0 mL)+lidocaine 2% (2.0 mL)			44.5 (32-54)‡	11 (64.7)	ND	7.7±1.3*	60.0±11.9¶
Elizondo-Rodríguez et al[31]	Randomized, double-blind, controlled	Heel pain at the insertion of the plantar fascia	6 mo	21	BTX-A	200 U (2.0 mL)	Origin of the plantar fascia and tender region	Yes	44.0±12.5	13 (57)	31.4±5.5	8.0±1.5*	77.6±15.5¶
				21	Corticosteroid	Betamethasone 3 mg/mL (1.0 mL)			46.4±11.0	19 (76)	29.7±4.8	7.7±1.9*	83.9±13.4¶
				18	Anesthetic	Ropivacaine 7.5 mg/dL (5.0 mL)			49.3±10.6	13 (57)	30.2±2.9	7.9±1.2*	84.6±12.1¶
Huang et al[14]	Randomized, double-blind, placebo-controlled	Chronic plantar fasciitis	3 mo	25	BTX-A	50 U (1.0 mL)	Origin of the plantar fascia	Yes	54.4±9.6	19 (76)	ND	5.9±0.9*	ND
				25	Normal saline	1.0 mL			51.5±5.5	19 (76)	ND	5.4±0.6*	ND
Peterlein et al[17]	Randomized, double-blind, placebo-controlled, multicenter	Chronic plantar fasciitis	18 wk	20	BTX-A	200 U (2.0mL)	Origin of the plantar fascia	No	52.4††	17 (85)	ND	ND	ND
				20	Normal saline	2.0 mL			51.8††	15 (75)	ND	ND	ND
Roca et al[18]	Randomized, open-label	Chronic plantar fasciitis	31-59 d	36	BTX-A	100 U (1.0mL)	Origin of the plantar fascia	No	54.4±13.3	25 (69.4)	30.9±5.4	7.0 (6.0-8.0)*,‡‡	ND
				36	ESWT	One session, 15 min, 3000 focused shock waves, flux intensity 12 mJ/mm^2, pressure 64 mPa, frequency 4 Hz	Site of maximum local tenderness		50.4±9.5	28 (77.8)	29.0±4.8	7.0 (5.0-8.0)*,‡‡	ND
Samant et al[21]	Randomized, double-blind, controlled	Chronic plantar fasciitis	12 mo	25	BTX-A	100 U (2.5 mL)	Injection into the origin of the plantar fascia	Yes	43.9±6.52	16 (64.0)	ND	8.7±0.9*	ND
				25	Corticosteroid	Methylprednisolone 40 mg/mL (2.0 mL) +lignocaine 2% (2.0 mL)			43.3±6.84	14 (56.0)	ND	9.1±0.8*	ND

NOTE. Values are expressed as mean ± SD unless otherwise indicated.
* VAS.
† AOFAS.
‡ Mean (range).
§ FAAM.
‖ Median (range).
¶ MFS.
# FHSQ, pain.
** FHSQ, function.
†† Mean only.
‡‡ Median (IQR).
Abbreviations: AOFAS, American Orthopaedic Foot and Ankle Society; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ESWT, extracorporeal shockwave therapy; FAAM, Foot and Ankle Ability Measures; IBTA, incobotulinum toxin A; MFS, Maryland Foot Score; NA, not applicable; ND, no data; US, ultrasound.

Fig 2 Risk-of-bias assessment of the included studies according to the Cochrane guidelines.

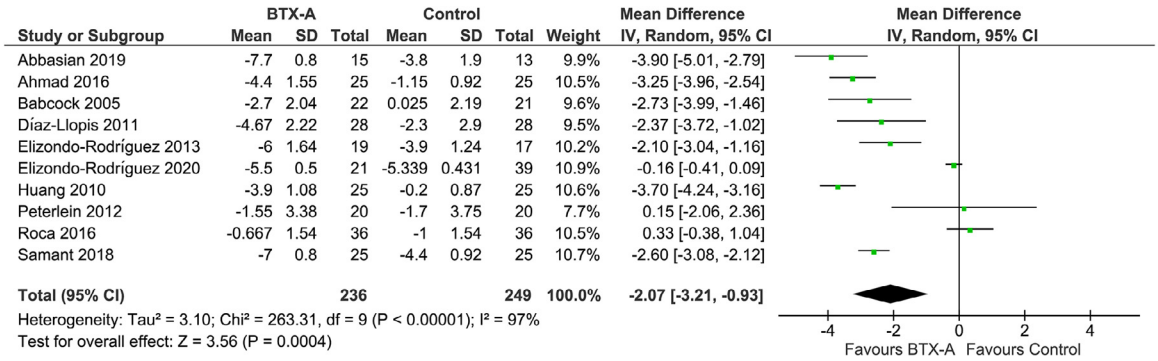

Fig 3 Forest plot displaying the mean difference and 95% CI for the effect of BTX-A injections on pain.

Table 2 Results of leave-1-out sensitivity analysis for pain

	Statistics With Study Removed		
Study Removed	Total MD (95% CI)	*P* Value	I^2 (%)
Abbasian et al[20]	−1.87 (−3.05 to −0.69)	.002	97
Ahmad et al[16]	−1.93 (−3.14 to −0.73)	.002	97
Babcock et al[13]	−2.00 (−3.21 to −0.79)	.001	97
Díaz-Llopis et al[15]	−2.04 (−3.25 to −0.82)	.001	97
Elizondo-Rodríguez et al[30]	−2.06 (−3.30 to −0.83)	.001	97
Elizondo-Rodríguez et al[31]	−2.33 (−3.29 to −1.36)	<.0001	92
Huang et al[14]	−1.88 (−2.99 to −0.76)	.001	96
Peterlein et al[17]	−2.26 (−3.45 to −1.06)	.0002	97
Roca et al[18]	−2.35 (−3.57 to −1.12)	.0002	97
Samant et al[21]	−2.00 (−3.29 to −0.71)	.002	97

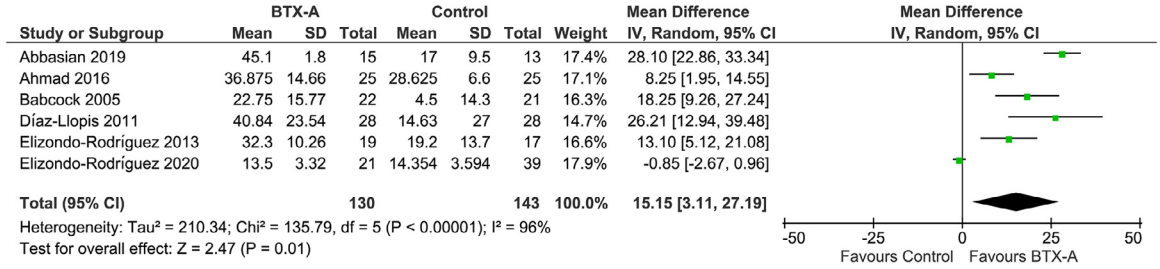

Fig 4 Forest plot displaying the mean difference and 95% CI for the effect of BTX-A injections on function.

Table 3 Results of leave-1-out sensitivity analysis for function

	Statistics With Study Removed		
Study Removed	Total MD (95% CI)	*P* Value	I^2 (%)
Abbasian et al[20]	11.96 (2.35-21.56)	.01	91
Ahmad et al[16]	16.66 (1.64-31.68)	.03	97
Babcock et al[13]	14.57 (1.05-28.08)	.03	97
Díaz-Llopis et al[15]	13.24 (0.34-26.14)	.04	97
Elizondo-Rodríguez et al[30]	15.61 (1.58-29.64)	.03	97
Elizondo-Rodríguez et al[31]	18.49 (9.72-27.27)	<.0001	85

Characteristics of included studies

A total of 485 individuals were recruited from 10 RCTs, including 236 in the BTX-A group and 249 in the control group. Almost all studies had a parallel double-blind design, except 1 single-blind study[15] and another with an open-label[18] fashion. The follow-up period within the studies varied from 31 days[18] to 12 months.[16,20,21] The doses and volume of the injected BTX-A ranged from 50 U[14] to 250 U[30] and from 0.7 mL[13] to 2.5 mL,[15] respectively. The anatomic region where the BTX-A was applied was also different among studies; most of them reported the application was directly or near the plantar, while 2 indicated that the injection was administered in the calf muscles (gastrocnemius and soleus).[20,30] Table 1 exhibits the complete characteristics of the selected studies.

Risk of bias assessment

All the included studies were cataloged with some concerns for the randomization process domain; only 1 trial was classified with a low risk of bias.[17] For the deviations from the intended interventions parameter, 6 studies showed a low risk of bias,[13,14,16,20,21,31] 3 studies had some concerns,[15,17,30] and 1 study exhibited a high risk of bias.[18] All studies were listed as low risk of bias for the missing outcome data, measurement of the outcome, and selection of the reported result domains. Finally, the selected studies were classified as some concerns for the overall bias parameter, except 1 study that showed a high risk of bias.[18] The Cochrane risk of bias assessment is shown in fig 2.

Effect of BTX-A injections on plantar fasciitis

Pain. Meta-analysis of 10 treatment arms showed a significant improvement in pain after BTX-A therapy (MD, −2.07 [95% CI, −3.21 to −0.93]; *P*=.0004; I^2=97%) (fig 3), and this effect size was robust in the sensitivity analysis (table 2). Furthermore, the calculated change obtained for pain relief after BTX-A intervention (Δ=2.07) was higher than the established MCID on the VAS for average pain (0.8 and 0.9cm) and the MCID for pain of first step (1.9cm).

Function

Six studies reported functional outcomes in a total of 273 patients (130 in the BTX-A intervention and 143 in the control group). A significant functional improvement was revealed after meta-analysis in favor of BTX-A injections (MD, 15.15 [95% CI, 3.11-27.19]; *P*=.01; I^2=96%) (fig 4). The effect size was robust in the sensitivity analysis (table 3). Additionally, the calculated change for functional improvement (Δ=15.15) was higher than the MCID reported in the FHSQ function subscale (7 points).

A subanalysis according to the treatment duration was performed. A significant pain relief was detected at 0-6 months and 12 months after BTX-A treatment; on the other hand, this subanalysis indicated a significant functional improvement at 0-6 months (supplemental table S1, available online only at http://www.archives-pmr.org/).

Plantar fascia thickness

Four studies assessed plantar fascia thickness involving a total of 232 individuals (107 in the BTX-A therapy and 125 in the control group). Meta-analysis demonstrated no significant changes in the plantar fascia thickness after BTX-A intervention (MD, −0.56 mm [95% CI, −1.24 to 0.12]; *P*=.11; I^2=94%) (fig 5).

Publication bias

Visual inspection of the generated funnel plot denotes a possible asymmetry for pain, suggesting a potential publication bias in the included studies (supplemental fig S1, available online only at http://www.archives-pmr.org/). The funnel plot for function and fascia thickness was not generated following the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions.*[28]

Discussion

The current meta-analysis of RCTs indicated that BTX-A leads to a statistically and clinically significant improvement of pain

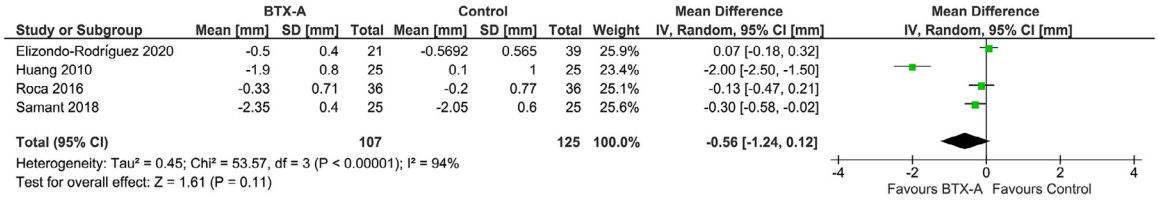

Fig 5 Forest plot displaying the mean difference and 95% CI for the effect of BTX-A injections on plantar fascia thickness.

and function in patients with plantar fasciitis. These results remained robust after sensitivity analysis for both clinical outcomes. However, our findings also revealed no beneficial effect on plantar fascia thickness after BTX-A therapy. We compared the total mean change for pain and function against available MCID in plantar fasciitis; in both outcomes, the mean change of our study was higher than the established MCID. The MCID for average pain (VAS) has been reported in 8 mm[32] and 9 mm,[33] while a change of 19 mm has been reported for pain on first step.[32] Regarding function, the MCID for the FHSQ function subscale was reported with a value of 7 points (considering a scale of 0-100).[32,33]

In agreement with previous meta-analyses,[19,34] our results indicate that BTX-A is effective in reducing pain in both the short- (0-6 months) and long-term (12 months). Additionally, we also found that an important functional improvement may be achieved at 6 months. Notably, the improvement in pain and function can be considered clinically meaningful.

It appears to be that plantar fascia thickening is a disorder commonly found in chronic plantar fasciitis.[35] However, it is not clear if change in the thickness of the plantar fascia is a target measurement to assess therapies effectiveness.[36-38] Changes in functional scores and their association with a decrease of fascial thickening are inconclusive.[14,31,38] Results of the current meta-analysis do not suggest a positive effect of BTX-A in plantar fascia thickening; however, the evidence is still insufficient, and further clinical trials evaluating this aspect are required.

Over the last years, the use of BTX-A to treat several health problems has been increasing. BTX-A reversibly inhibits the presynaptic release of neurotransmitters at the neuromuscular junction for prolonged periods causing muscle relaxation.[39] A previous study showed that BTX-A also has anti-inflammatory properties on the soft tissue where it is injected.[40] In this regard, it has been hypothesized that the application of BTX-A might be a therapeutic option for plantar fasciitis. Evidence from experimental studies in animal models suggests that BTX-A may improve pain and inflammation through different mechanisms of action.[41,42] Specifically, BTX-A inhibits neurogenic inflammation mediators such as substance P and calcitonin gene-related protein in animal models with acute and chronic inflammation.[43-45] Also, BTX-A blocks the activation of interleukin 1 (an important proinflammatory cytokine) by inhibiting the G protein family.[41] Despite previous research, the potential antinociceptive mechanism of the BTX-A is still inconclusive.[42,46]

Study limitations

Our meta-analysis exhibit a number of limitations. First, given that the sample size of the selected clinical was small, the overall population of the present meta-analysis resulted in a limited number of individuals. Second, because our meta-analysis exhibited a high interstudy heterogeneity, we performed a random-effects model and a subgroup analysis by treatment duration to minimize this aspect. BTX-A was compared with active control groups in several studies, which may have affected our findings. Furthermore, the site of injection and the use or not of ultrasound-guided injections may also account for potential sources of interstudy heterogeneity. Finally, because the information related to adverse events was not provided in most of the included trials, this outcome was not assessed.

Conclusions

In summary, our results suggest that treatment of plantar fasciitis with BTX-A injections is effective in relieving pain in the long-term and improving function in the short-term. However, there was no beneficial effect of this therapy on the plantar fascia thickness.

Suppliers

a. Distiller SR; Evidence Partners.
b. Review Manager V5.3; The Cochrane Collaboration.

Keywords

Botulinum toxins, type A; Fasciitis, plantar; Meta-analysis; Pain; Rehabilitation; Systematic review

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Supplemental Appendix S1

Search Strategies

Ovid

EBM Reviews - Cochrane Central Register of Controlled Trials <Dec 2020>

EBM Reviews - Cochrane Database of Systematic Reviews <2005 to Dec 21, 2020>

Embase <1974 to 2020 Dec 22>

Ovid MEDLINE(R) ALL <1946 to Dec 22, 2020>

1 ("Chronic Plantar Fasciitis" or "Fasciitis, Chronic Plantar" or "Fasciitis, Plantar, Chronic" or "Heel Spur Syndrome" or "Heel, Policeman's" or "Heels, Policeman's" or "Plantar Fasciitis" or "Plantar Fasciitis, Chronic" or "Policeman Heel" or "Policeman's Heel" or "Policeman's Heels" or "Policemans Heel" or "Fasciitis, Plantar" or "Heel Spur" or "calcaneal spur syndrome" or "fasciitis, plantar" or "heel spur syndrome").mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, fx, dq, nm, kf, ox, px, rx, an, ui, sy] 4975
2 exp botulinum toxin/ 35938
3 ("Botulin" or "Botulinum Toxin" or "Clostridium botulinum Toxins" or "Botulinum Toxins" or "Botulinum Toxins, Type A" or "Botox" or "Botulinum A Toxin" or "Botulinum Neurotoxin A" or "Botulinum Toxin Type A" or "Clostridium botulinum A Toxin" or "Clostridium Botulinum Toxin Type A" or "Meditoxin" or "Neuronox" or "Oculinum" or "Onabotulinumtoxin A" or "OnabotulinumtoxinA" or "Vistabel" or "Vistabex" or "botulinal toxin test" or "botulinium toxin" or "botulinum neurotoxin" or "botulinum toxins " or "botulinus toxin" or "botulism toxin" or "clostridium botulinum exotoxin" or "clostridium botulinum toxin").mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, fx, dq, nm, kf, ox, px, rx, an, ui, sy] 66554
4 2 or 3 66554
5 1 and 4 146
6 EBM Reviews - Cochrane Central Register of Controlled Trials <December 2020> 26

EBM Reviews - Cochrane Database of Systematic Reviews <2005 to December 22, 2020> 2

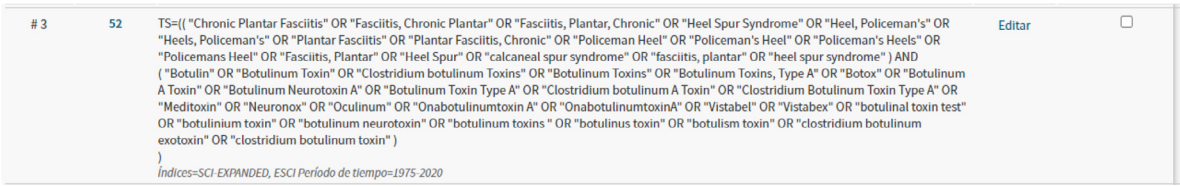
Embase <1974 to 2020 Week 42> 82

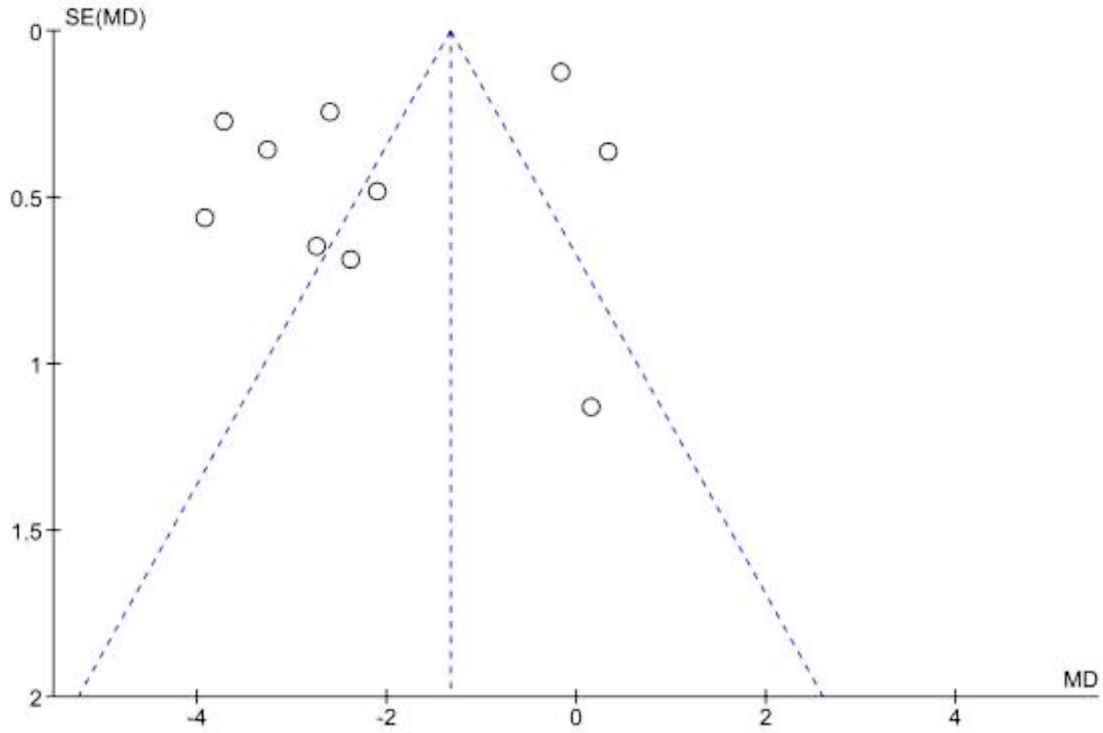
Ovid MEDLINE(R) ALL <1946 to December 21, 2020> 36

Scopus

("Chronic Plantar Fasciitis" OR "Fasciitis, Chronic Plantar" OR "Fasciitis, Plantar, Chronic" OR "Heel Spur Syndrome" OR "Heel, Policeman's" OR "Heels, Policeman's" OR "Plantar Fasciitis" OR "Plantar Fasciitis, Chronic" OR "Policeman Heel" OR "Policeman's Heel" OR "Policeman's Heels" OR "Policemans Heel" OR "Fasciitis, Plantar" OR "Heel Spur" OR "calcaneal spur syndrome" OR "fasciitis, plantar" OR "heel spur syndrome") AND ("Botulin" OR "Botulinum Toxin" OR "Clostridium botulinum Toxins" OR "Botulinum Toxins" OR "Botulinum Toxins, Type A" OR "Botox" OR "Botulinum A Toxin" OR "Botulinum Neurotoxin A" OR "Botulinum Toxin Type A" OR "Clostridium botulinum A Toxin" OR "Clostridium Botulinum Toxin Type A" OR "Meditoxin" OR "Neuronox" OR "Oculinum" OR "Onabotulinumtoxin A" OR "OnabotulinumtoxinA" OR "Vistabel" OR "Vistabex" OR "botulinal toxin test" OR "botulinium toxin" OR "botulinum neurotoxin" OR "botulinum toxins " OR "botulinus toxin" OR "botulism toxin" OR "clostridium botulinum exotoxin" OR "clostridium botulinum toxin")

WoS





Supplementary fig S1 Funnel plot displaying publication bias in the studies reporting the effect of BTX-A injections over pain in plantar fasciitis.

Supplementary table S1 Effect of BTX-A injections pain and function in clinical trials stratified by treatment duration 0-6 mo and 12 mo.

Outcome	Clinical Trials Evaluating the Outcome (n)	MD [95% CI]	*P*-Value (Test for Overall Effect)
Pain			
0-6 months	7	-1.54 [-2.97, -0.12]	0.03
12 months	3	-3.12 [-3.82, -2.42]	<0.00001
Function			
0-6 months	4	13.33 [0.31, 26.34]	0.04
12 months	2	18.26 [-1.20, 37.71]	0.07

BTX-A, botulinum toxin A; MD, mean difference; CI, confidence interval.