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Hand

Toxin for Treating Raynaud Conditions in Hands (The TORCH Study): A Systematic Review and Meta-analysis

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Background: Raynaud disease of the hands is a complex disorder resulting in inappropriate constriction and/or insufficient dilation in microcirculation. There is an emerging role for botulinum toxin type A (BTX-A) in the treatment armamentarium for refractory Raynaud disease. The aim of this systematic review was to critically evaluate the management of primary and secondary Raynaud disease treated with BTX-A intervention.

Methods: We performed a Preferred Reporting Items for Systematic Reviews and Meta-Analyses-compliant systematic review of clinical studies assessing treatment of primary or secondary Raynaud disease with BTX-A by searching Ovid MEDLINE and Embase databases from inception to first August 2023. The review protocol was prospectively registered on the PROSPERO database (CRD42022312253).

Results: Our search strategy identified 288 research articles, of which 18 studies [four randomized controlled trials (RCTs), two non-RCTs, five case series, and seven retrospective cohort studies] were eligible for analysis. Meta-analysis demonstrated that the probability of pain visual analog scale score improvement with BTX-A intervention was 81.95% [95% confidence interval (74.12–87.81) $P = 0.19$, heterogeneity $I^2 = 26\%$] and probability of digital ulcer healing was 79.37% [95% confidence interval (62.45–89.9) $P = 0.02$, heterogeneity $I^2 = 56\%$].

Conclusions: Delivery of BTX-A to digital vessels in the hand may be an effective management strategy for primary and secondary Raynaud disease. A definitive, appropriately-powered RCT with objective functional and patient-reported outcome measures is required to accurately assess and quantify the efficacy of BTX-A in Raynaud disease of the hands. *(Plast Reconstr Surg Glob Open 2024; 12:e5885; doi: 10.1097/GOX.0000000000005885; Published online 14 June 2024.)*

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INTRODUCTION

Raynaud phenomenon (RP) was first discovered in 1834 by Maurice Raynaud, who described a neuroendothelial dysregulation in the vessels supplying the digits of the hands and feet.[1,2] It is a common condition that affects approximately 5% of the general population and is characterized by episodic arterial vasospasm in the digits, resulting in a triad of pallor followed by cyanosis and redness with pain.[3] Severe cases can result in digital ulceration and localized tissue necrosis. These scenarios can be further complicated by osteomyelitis, gangrene, and autoamputation, ultimately impairing hand function and negatively impacting quality of life.[3] RP is typically triggered by a cold environment or emotional stressors. Although the underlying pathophysiological mechanisms of RP remain unclear, accumulating evidence suggests that upregulated

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vascular smooth muscle α2C adrenergic receptors may play an important role. This most likely occurs through inducing hyperfunction of the sympathetic nervous system, causing arteriole vasoconstriction.[4,5]

Raynaud disease is traditionally managed by a variety of pharmacological therapies. The drug classes typically prescribed include calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, prostaglandins, other vasodilators, sympatholytic agents, and thromboxane A2 inhibitors.[3] Symptoms are often refractory to medical management, and surgical interventions are required. However, surgical interventions such as sympathetic trunk transection and digital sympathectomy are fraught with complications, including compensatory hyperhydrosis and disease recurrence, respectively.[6] To bridge this therapeutic window, there is an emerging role for local delivery of botulinum toxin type A (BTX-A) in the treatment armamentarium for this condition.

BTX-A is a neurotoxin that acts on presynaptic nerve terminals to eliminate cholinergic nerve transmission by cleaving the SNAP-25 protein[6,7] and has been used in the treatment of RP refractory to medical treatment for some time.[8,9] Recently, data from preclinical studies have shown that BTX-A can inhibit arteriole vasoconstriction in a dose-dependent manner by cleaving SNAP-25 in sympathetic neurons. The mechanism underlying this response was shown to be blocked vesicle fusion with the presynaptic membrane after BTX-A treatment, inhibiting the release of noradrenaline.[5] This response was corroborated by the findings of other recent clinical studies which show that BTX-A treatment can improve symptoms in patients living with RP by reducing the frequency of vasospastic episodes and time to digital ulcer healing as well as improving hand function.[7,10]

Rationale

To date, there has been no critical evaluation of the quality of the evidence assessing use of subcutaneous BTX-A intervention for Raynaud disease of the hand or whether the available evidence supports its effectiveness. This systematic review of BTX-A intervention for primary and secondary Raynaud disease of the hands provides an objective assessment of the evidence, a descriptive analysis of its effectiveness and a meta-analysis to assess the probability of patient-reported functional improvement.

Objectives

- To examine the available literature and determine if BTX-A represents an effective management strategy for primary and secondary Raynaud disease of the hands.
- To provide evidence for the design of a randomized controlled trial (RCT) exploring the effectiveness of BTX-A in primary and secondary Raynaud disease of the hands.

Methods

The objective of this review was to assess the literature on use of BTX-A in the treatment of primary and secondary Raynaud disease of the hands with a focus on identifying and evaluating outcome measures, using the methodology described in the *Cochrane Handbook of Systematic Reviews of Interventions*, where applicable. This review has been performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10] A comprehensive review protocol was prospectively registered on the PROSPERO data (CRD42022312253).

Search Methods

Studies were identified through a systematic literature search, facilitated by a medical librarian, of all records in Ovid MEDLINE and Ovid Embase since database inception to August 1, 2023. Both "free-text term" and "MeSH term" searches were performed by combining variations of keywords "Raynaud's disease," "Raynaud's phenomenon," and "Botulinum toxin type-A" using Boolean operators. The results for these search terms were merged. Duplicate citations were discarded, and only articles in English were included for review. The full text of each shortlisted article was read in full by two authors (E.G. and R.D.) independently to assess eligibility for inclusion. The final list of included studies was compared and discussed between the two reviewers, and a supervisor (J.W.) mediated any disparities. Disparities that arose regarding inclusion of articles were resolved by consensus with reference to the prespecified inclusion criteria. The published data from included articles were evaluated for reporting of relevant outcomes.

Criteria for Study Selection

Criteria for study selection was defined during the protocol stage. Two authors (E.G. and R.D.) used a prespecified inclusion/exclusion spread-sheet to independently assess study eligibility. Study participants were adults with primary and/or secondary Raynaud disease of the hands who underwent BTX-A treatment. Case reports, letters, editorials, anatomical studies and literature reviews were excluded. Studies of participants with vasculopathies other than RP or with management other

Takeaways

Question: The aim of this systematic review was to critically evaluate the management of primary and secondary Raynaud disease with BTX-A intervention.

Findings: Meta-analysis demonstrated that the probability of pain visual analog scale score improvement with BTX-A intervention was 81.95% [95% confidence interval (74.12–87.81) $P = 0.19$, heterogeneity $I^2 = 26\%$] and probability of digital ulcer healing was 79.37% [95% confidence interval (62.45–89.9) $P = 0.02$, heterogeneity $I^2 = 56\%$].

Meaning: This systematic review precedes an imminent randomized controlled trial assessing the efficacy and mechanistic effects of botulinum toxin in the treatment of Raynaud conditions of the hand. The review has highlighted the issues with a lack of focus on patient-reported outcome measures, and we planned to address this in an appropriately designed randomized controlled trial.

than BTX-A were excluded. Studies were included if they reported functional or patient-reported outcomes following management of RP with the use of BTX-A. Search terms included the following: "botulinum toxin-A" + "Raynaud's"±(i) "primary" (ii) "secondary" (iii) "disease" (iv) "phenomenon/syndrome" (v) "treatment" and (vi) "management."

Data Analysis

Data collection was carried out in accordance with the methodology described in the *Cochrane Handbook of Systematic Reviews of Interventions* where applicable. Data collected were extracted into a predesigned electronic form. Two authors (E.G. and R.D.) extracted data independently and checked the data set for accuracy. Primary outcomes assessed included the following patient-reported outcome measures: pain visual analogue scale (VAS) score, Disabilities of the Arm, Shoulder, and Hand (DASH) score, and Raynaud Condition Score (RCS). Secondary outcomes included healing of digital ulcers, frequency of exacerbated vasospastic episodes, digital edema, cold intolerance, skin temperature, velocity of digital blood flow, and perfusion of the digits. For parameters assessing perfusion, we included studies reporting outcomes from noninvasive laser Doppler imaging, digital pulse pressures, and thermal camera imaging.

Statistical Analysis

We performed a descriptive analysis to summarize the outcomes as follows: the VAS, DASH questionnaire, RCS, digital temperature, arterial flow velocity, digital pulse pressures, digital thermography, digital ulcer healing, digital edema, cold intolerance, and frequency of vasospastic episodes.

Study heterogeneity limited comparative cohorts to only two outcome measures. Meta-analysis of proportions was performed to determine pooled proportions for ulcer healing and improvement in VAS score. VAS was dichotomized to either "improved" or "not improved" to facilitate data synthesis across heterogenous studies. Statistical software platform "R" version 4.0.3 (2020-10-10) was used with the "meta" (version 5.2-0) and "metafor" (version 3.4-0) packages. Statistical heterogeneity was assessed using the χ^2 test ($P < 0.10$ = statistically significant heterogeneity) and the I^2 measure.[11] There was no prespecified I^2 cutoff for pooling. Random-effects models are reported. Summary statistics are reported as proportions (%) with 95% confidence intervals (CIs).

Results

Search Strategy

Our search strategy identified 288 research articles, 95 of which were relevant to the question eligible for screening. Of the 95 articles, 39 were read in full, and 18 studies were deemed eligible for inclusion after screening of title and/or abstract.[7,10,12–27] Data were immediately available for collection from the 18 studies identified. Details of excluded articles are illustrated in the PRISMA flowchart (Fig. 1).[28]

Study Characteristics

The included studies were published between 2007 and 2023. (**See table, Supplemental Digital Content 1**, which shows characteristics of N = 18 included studies. **http://links.lww.com/PRSGO/D270**.) Four studies were RCTs, and two studies were non-RCTs. Seven studies were retrospective cohort studies, and five studies were case series. The follow-up period ranged from 0.5 to 93 months (mean follow-up of 11.8 months). Studies varied from two to 90 participants. There was global representation from studies: six studies were from research groups in the United States, three from the United Kingdom, four from Europe (France, Netherlands, and Spain), and four from other countries (Taiwan, Japan, China, Iran, and India). The mean sample size was 22 participants (range: 4–48).

Risk of Bias

Study quality was assessed using the Cochrane Risk of Bias for RCTs and the National Institute of Health tool for nonrandomized control trials, prospective case series, and retrospective study designs.[11] (**See table, Supplemental Digital Content 2,** which shows quality assessment for included studies. **http://links.lww.com/PRSGO/D271**.) The aforementioned scoring systems were used for each study to result in an overall rating of study quality as "good," "fair," or "poor."[11] Over half of the studies (10/18; 55.5%) on BTX-A use in Raynaud disease of the hands were single center observational studies. Overall, a "good" National Institute of Health score was established for the case control studies and case series analyzed in this systematic review. Although these studies reported improvements in patients' Raynaud disease, the outcome measures assessed were variable throughout the 18 studies assessed. The overall standard of the four RCTs assessed as per the Cochrane risk of bias tool was deemed "good."

Pain Score Outcomes

Fifteen studies assessed pain as an outcome measure following treatment with BTX-A (83.3% of all studies). Improvement in pain was determined in 12 studies using the VAS score, which recorded mean pain improvement for each study. Improvement in VAS post BTX-A treatment ranged from 36% to 100% (mean: 83.7%, SD: 19.9), with four studies demonstrating 100% improvement in pain.[7,10,12–14,17,21–26] The overall mean VAS score improvement was 4.11 ± SD 2.4. Three further studies reported pain improvement as a dichotomous "yes" or "no" or another nondisclosed pain scale.[21,23] The remaining two studies showed no improvement in pain following treatment with BTX-A.[19,27] Meta-analysis of dichotomized VAS scores (improved versus not improved) suggests that the probability of pain score improvement with the use of BTX-A is 81.95% [95% CI (74.12–87.81) $P = 0.19$, heterogeneity $I^2 = 26\%$; Fig. 2].

Digital Ulcer Healing Outcomes

Ten studies assessed digital ulcer healing as an outcome measure following treatment with BTX-A (55.6% of all

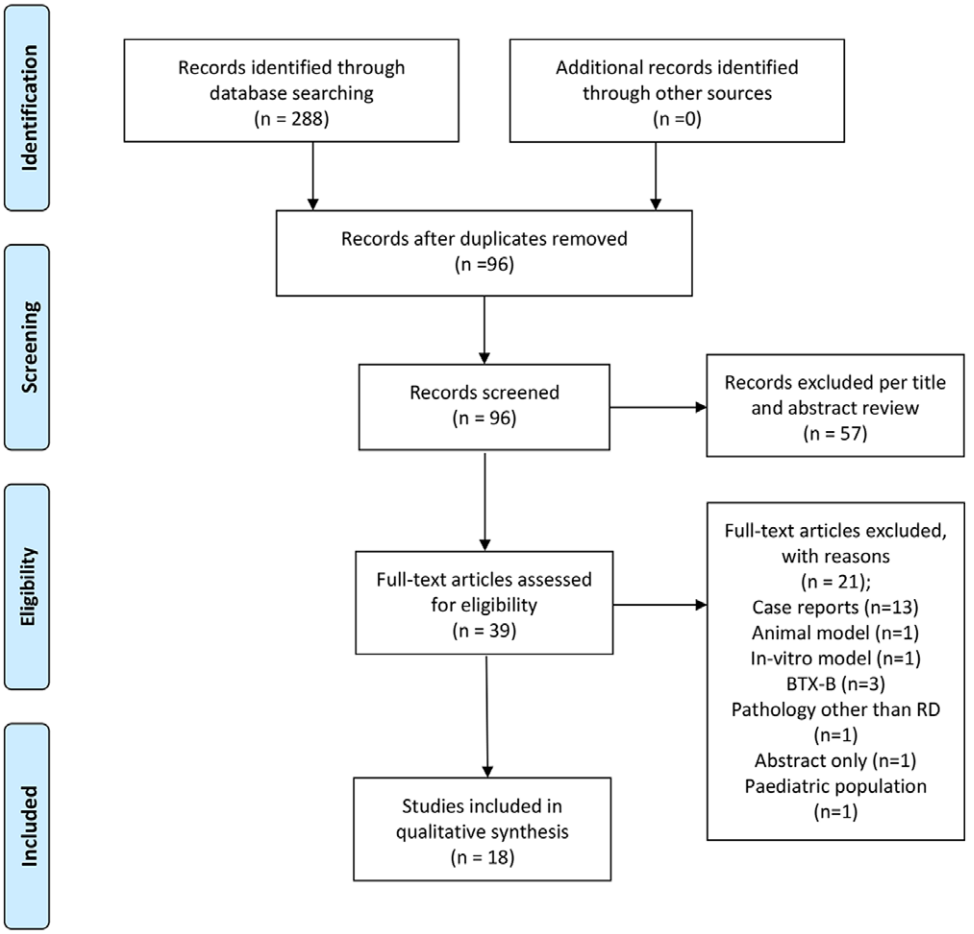

Fig. 1. PRISMA flowchart: breakdown of the articles analyzed for inclusion.

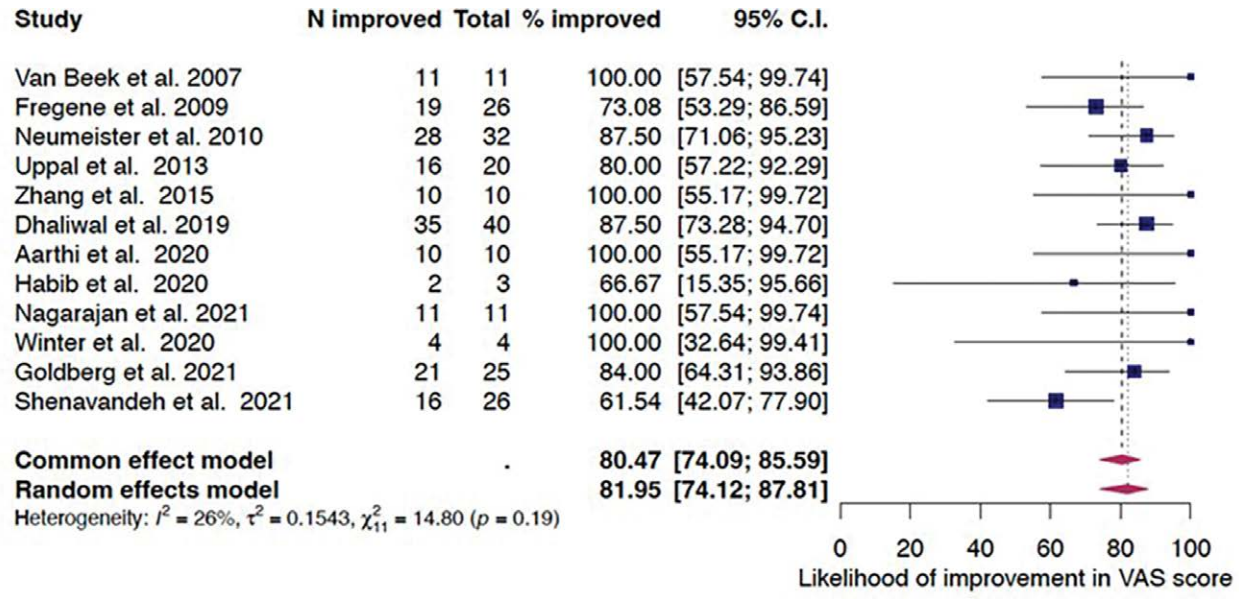

Fig. 2. Meta-analysis: likelihood of improvement in VAS score.

studies).[7,10,12–14,16–18,25,29] Digital ulcer healing was recorded in all studies as a percentage improvement. Percentage healing ranged from 47% to 100% (mean: 88.1%, SD: 17.6), with six studies demonstrating 100% ulcer healing post treatment with BTX-A. Meta-analysis suggests that the likelihood of digital ulcer healing rate following BTX-A treatment is 79.37% [95% CI (62.45–89.90) $P = 0.02$, heterogeneity $I^2 = 66\%$; Fig. 3].

Further Outcome Measures

Additional generic and/or disease-specific patient-reported outcome measures were inconsistently reported across studies. Nine studies reported reduction in vasospastic episodes following treatment with BTX-A. However, the heterogeneity in reporting (time between episodes, frequency of episodes, resolution of episodes) precluded inclusion in the meta-analysis.[7,10,12–27] Eight studies reported improvement in hand temperature following treatment with BTX-A. Most of these studies showed patient-reported subjective increases in the perceived temperature of their hands and only one study demonstrated an increase in digital pulp temperature by 1.3°C at latest follow-up.[10,15]

DISCUSSION

This article is a PRISMA-compliant systematic review and meta-analysis of the use of subcutaneous BTX-A injections for treatment of Raynaud disease of the hands.[28] It provides a critical synthesis of the published literature with particular attention to patient-reported outcome measures and clinical symptoms following treatment with BTX-A. Overall, our review suggests that BTX-A leads to symptomatic benefits in patients with Raynaud disease of the hands. Across all studies, a positive effect from intervention was observed. However, the variety in design and methodology of the included studies, inconsistent outcome reporting, and lack of standardization of injection sites and doses administered, prevents this review from definitively supporting or refuting the hypothesis that BTX-A is an effective method of treatment for symptom control in Raynaud disease of the hands.

This review supports an overall likelihood of improvement in patient-reported pain following treatment with BTX-A with a pool average of 81.95% of study participants reporting improvement in symptoms (Fig. 2). Five studies in the review report 100% improvement in pain scores post treatment with BTX-A.[12,17,24,25] However, inconsistency in reporting across studies lead to dichotomization of VAS scores into two groups (improved, not improved) for the purpose of analysis. This may have contributed to the lack of statistical significance within the pooled analysis. Surprisingly, two double-blinded placebo-controlled RCTs within this review reported no statistically significant improvement of pain scores post treatment with BTX-A. Bello et al[19] investigated the therapeutic effect of BTX-A specific to a group of 40 cases of scleroderma-associated Raynaud disease inclusive of both limited and diffuse scleroderma patients. Overall minimal improvements in pain were reported; however, it is likely that the heterogeneity of disease severity (limited versus diffuse scleroderma) and small sample size precluded statistical significance. Senet et al[27] investigated the efficacy of BTX-A treatment for systemic sclerosis–associated RP (SSc-RP) in a multi-center trial involving 46 patients. The inability of BTX-A to consistently improve SSc-RP patient-reported outcomes may be multimodal and reflective of the endothelial damage and remodeling or the perivascular inflammation that characterizes systemic sclerosis. These changes may induce resistance to the biologic effect of BTX-A on vessels resulting in a subtherapeutic treatment effect.[30]

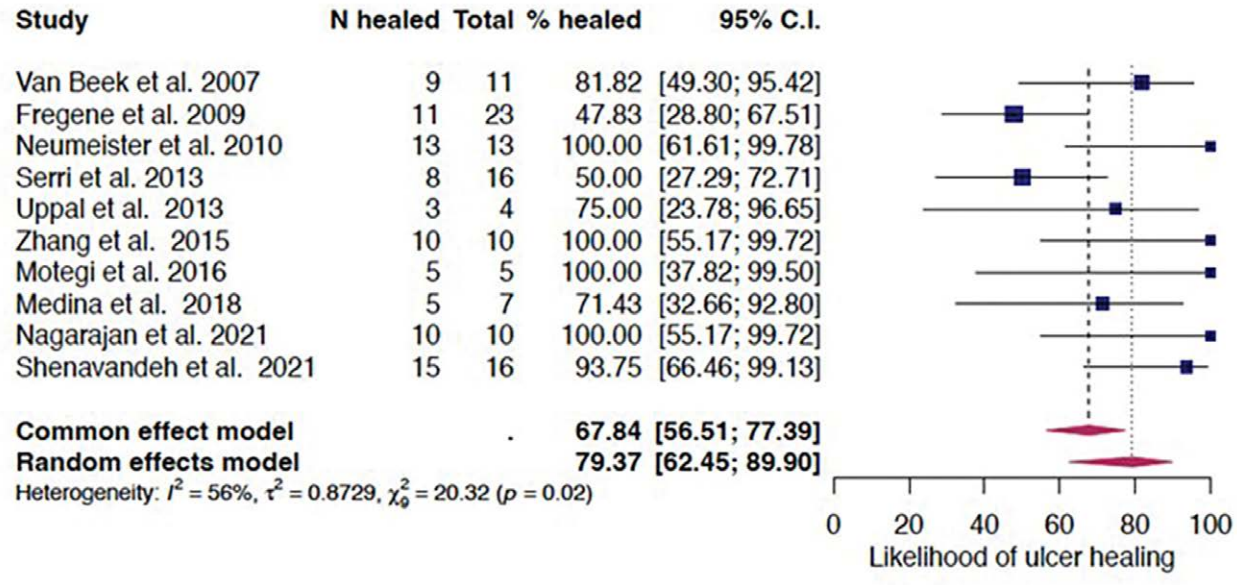

Fig. 3. Meta-analysis: likelihood of improvement in ulcer healing with the use of BTX-A.

Likelihood of digital ulcer healing following treatment with BTX-A estimated a pooled average of 79.4% (P = 0.02). All studies demonstrated improvement in digital ulcer healing, and six studies reported 100% resolution of digital ulceration. The mechanistic evidence to support this strong therapeutic effect of BTX-A remains unclear, given the discrepancy seen in vascular flow and perfusion outcomes post treatment with BTX-A.[31] The use of thermal imaging to assess the effect of BTX-A has illustrated skin surface temperature recovery after cold water stimulation at 4 weeks after injection.[18] One study illustrated significant improvement in hand temperature at 6 weeks post injection, but this was not sustained at 3-months follow-up.[21] Three studies assessed digital arterial perfusion or flow. Blood flow velocity was demonstrated an increase from 30.5 (± 14.4) cm per second before to 45.1 (± 15.8) cm per second after treatment with BTX-A.[17] Laser Doppler imaging demonstrated a range of flow change from 48.15% to 317.39% in digits following BTX-A treatment.[9] However, contrary to the positive effect in these case series, the Bello et al RCT demonstrated reduction in perfusion by 30.08 flux units (7.7% from baseline) in patients allocated to the BTX-A group.[19] Absolute blood flow at 1-month follow-up was also lower versus those allocated to the placebo group (P = 0.018).[13] The therapeutic benefit of BTX-A in refractory acute digital ulceration, prevention of osteomyelitis, and digital preservation is well recognized in clinical practice.[29] Perhaps alternative modalities to capture the sensitivity of changes in digital perfusion and flow need to be explored.[32]

Strengths and Limitations

The conclusions drawn from studies assessed in this systematic review are limited by small sample sizes without evidence of preparatory power calculation, variability in BTX-A dose and site administration and unclear enrolment methods. The low power of the published data was a contributory factor to the relatively high heterogeneity reported from our meta-analysis. Only one RCT (Aarthi et al[22]) reported outcomes that could be included in the meta-analysis. This precluded a sensitivity analysis of RCTs.

This systematic review and meta-analysis is a PRISMA-compliant, prospectively registered, critical assessment of evidence base for BTX-A treatment in Raynaud disease of the hands.[28] We have focused on robust systematic review methodology to assess unbiased and scientific assessment of the body of knowledge for BTX-A use in Raynaud disease. Our search strategy, conducted by a medical librarian, included a broad range of study types to capture all relevant publications of primary clinical research, enabling a global evaluation of this topic. We performed a statistical meta-analysis granting insight into the likelihood of Raynaud disease symptom improvement with the use of BTX-A.

CONCLUSIONS

The current literature supporting the use of BTX-A for Raynaud disease of the hands is insufficient to provide reliable guidance for clinicians and patients. However, all 18 studies analyzed in our review suggest a beneficial effect of BTX-A at some level. However, the small sample sizes and the inconsistency of outcome reporting reduce the reliability of the findings reported. We suggest pre-RCT feasibility trials to inform injection protocols, minimum effective BTX-A dose concentrations and adequate powering of subcohorts (SSc-RP) to accurately design an RCT to assess the efficacy of BTX-A in Raynaud disease of the hands. In the meantime, BTX-A should be considered as part of the treatment armamentarium for Raynaud disease especially in the context of refractory acute digital ulceration in combination with meticulous surgical debridement of necrotic tissue.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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