Pharmacologic Treatment of Idiopathic Chilblains (Pernio): A Systematic Review

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Abstract

Idiopathic chilblains is a cold-induced inflammatory condition that causes significant morbidity. When preventative measures alone are inadequate, oral nifedipine is generally recommended as first-line pharmacologic therapy. Given the natural course of this spontaneously remitting/relapsing condition, controls are needed to critically appraise studies and determine the value of treatments. We report a systematic review of placebo-controlled or comparative therapeutic trials for the treatment of idiopathic chilblains. Our search of PubMed, Embase, and Cochrane databases, identified 11 studies that met our inclusion criteria for a combined study population *n* = 576. Therapies included nifedipine, pentoxifylline, tadalafil, topical glyceryl trinitrate (GTN), topical minoxidil, diltiazem, corticosteroids, and vitamin D. There was moderate evidence to support the use of nifedipine and pentoxifylline in the treatment of severe or refractory cases of idiopathic chilblains, while other therapies had inadequate evidence or nonsignificant results compared to placebo.

Keywords

chilblains, pernio, cold-induced, environmental, vasculopathy, nifedipine, pentoxifylline

Introduction

Idiopathic chilblains (pernio) is an inflammatory condition triggered by exposure to damp-cold weather. It is observed worldwide, but more frequently in colder climates such as the UK and Northwestern Europe.[1,2] There have been cases of familial clustering, and a case-control series showed a familial relative risk of 3.6, suggesting genetic predisposition.[3,4] Chilblains-like presentations have been observed in patients testing positive for coronavirus disease 2019 (COVID-19), although thought to occur through a different pathomechanism.[5]

The typical presentation of idiopathic chilblains involves single or multiple symmetrically distributed, erythrocyanotic lesions on the distal toes and fingers, and less commonly the heels, nose, and ears. Lesions range from red-blue macules to bullae and ulcers. Symptom onset occurs in the winter, with individual episodes lasting 1-3 weeks, and spontaneous resolution in the spring. Annual recurrences are common, and elderly patients or those with venous insufficiency may experience a protracted course.

Chilblains is generally not associated with systemic involvement; however, chilblains-like presentations can be associated with cryoglobulins or cold agglutinins. Differential diagnoses include raynaud's phenomenon, cold panniculitis, and chilblain lupus.

Treatment of chilblains primarily involves preventative measures, but severe and/or persistent cases may require pharmacologic therapy. There are relatively few clinical studies to guide treatment choice, although nifedipine is considered the mainstay of systemic treatment and is widely prescribed.[1,2] Other therapies with low-level evidence or anecdotal use, include corticosteroids, topical minoxidil, topical nitroglycerin, nicotinamide, and pentoxifylline.[1,2]

Given the natural course of spontaneous remission, it is difficult to assess the efficacy of treatment for chilblains without an objective control. Herein, we report a systematic review of placebo-controlled or comparative clinical trials for the treatment of chilblains.

Methods

Eligibility

Randomized controlled or comparative trials on patients with a clinical and/or histologic diagnosis of chilblains were included in our systematic review. Trials lacking a control or comparative group were excluded, as well as case series and

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case reports. Pharmacological therapy of chilblains was defined as those concerning the use of drugs; studies with non-drug therapies (ie, physical treatments) were excluded.

Search Strategy

PUBMED, EMBASE, and the Cochrane Database were searched for relevant studies performed in humans and published in English. No date limits were set. No limits on the total number of patients included were set. Search terms (MeSH headings) included: pernio, perniosis, chilblain; and Emtree: chilblain (pernio, perniosis). The search was conducted on March 14, 2019. Reference lists of included articles were hand-searched for any additional relevant studies. Duplicate articles were removed.

Data Extraction

Data were extracted and synthesized in tabular format, and triple checked for accuracy. The level of evidence (LOE) for each article was evaluated using the Oxford Center for Evidence-based Medicine scale.[6] Study quality was assessed using the U.S. Preventive Services Task Force quality rating criteria for randomized controlled trials (RCTs).[7]

Outcomes

Outcomes were improvement in chilblains signs and symptoms, as measured by clinical assessment(s) and/or patient completed questionnaire(s), including visual analog scales (VASs).

Results

The titles and abstracts of 381 articles identified through our search strategy were screened for inclusion by M.P. using our predetermined criteria (Figure 1). The full texts of selected articles ($n = 12$) were then independently assessed for inclusion in an unblinded fashion by M.P. and M.K. One article was excluded after full review,[8] since it was not an original RCT, and the results were previously published in an article already included in our analysis.[9] Thus, 11/381 articles ($n = 576$ recruited; $n = 510$ completed the studies) met eligibility criteria and were included in subsequent analysis. 9/11 studies were RCTs with LOE 1b (individual RCT) as per the Oxford scale, and 2/11 were LOE 2b (including lower quality RCTs). 9/11 studies had "good" and "fair" quality ratings as per the U.S. Preventive Services Task Force. 6/11 studies had a nifedipine treatment group, and 3/11 pentoxifylline. Additional therapies included topical glyceryl trinitrate, topical minoxidil, diltiazem, tadalafil, corticosteroids, and vitamin D. Due to heterogeneity of the designs and natures of the studies, in addition to the data, a meta-analysis was not possible.

Table 1 specifies the study-type, interventions, methods, outcomes, and limitations for the articles included in this systematic review of chilblains treatments. Table 2 summarizes the inclusion and exclusion criteria and the primary and secondary outcomes of the studies included in the studies, and Table 3 specifically highlights the frequency of side effects produced by the therapies.

Nifedipine

We identified six clinical trials supporting the use of nifedipine for the treatment of chilblains, including a randomized placebo-controlled trial performed by Dowd et al. in 1986 ($n = 10$) which compared nifedipine to a retard preparation,[9] and several randomized trials comparing nifedipine to (i) diltiazem ($n = 36$),[10] (ii) topical 5% minoxidil ($n = 52,84$),[11,12] (iii) topical glyceryl trinitrate ($n = 53$).[13]

Conflicting with these studies is a more recent 2016 randomized placebo-controlled trial ($n = 32$) that failed to show superiority to placebo.[14]

Dowd et al. demonstrated that 7/10 patients treated with nifedipine experienced resolution of lesions within 7-10 days.[9] During the crossover period, 5/10 patients initially treated with nifedipine had relapses within 1 week, and 3/5 had to be restarted on nifedipine. In the remaining 2/5 patients, and the 5 patients initially treated with placebo, new lesions continued to develop and slowly resolve 20-28 days from onset. No correction was made for changes in ambient temperature. Nifedipine side effects included dizziness, flushing, occasional headaches, and hypotension.

Patra et al. compared nifedipine vs diltiazem and demonstrated that 2/12 patients on diltiazem showed complete relief in 7 days, and 3/12 patients by the 14th day.[10] However, 7/12 cases showed little or no response by 7-10 days, so they were switched to the nifedipine group. In the nifedipine group ($n = 24$), 21 (88%) cases showed 80% to 90% relief by the fourteenth day. The authors concluded that nifedipine is more effective than diltiazem for the treatment of chilblains.

In 2010, Kubais et al. similarly published a single blind trial in Iraq.[11] After 2 weeks, 20 (57%) patients in the nifedipine group showed "good improvement" (complete regression of erythema and partial regression of edema), and 9(26%) showed "very good improvement"(complete regression of erythema, edema, vesicles, and ulcer), $P < .05$. In comparison, 6 (35%) patients in the minoxidil group showed good improvement and only 1(6%) very good improvement. In the nifedipine group, 19 (54%) patients reported flushing, 3(9%) had constipation, and 2(6%) had headache.

Khalid et al. (2014) further reported that 88% of patients treated with nifedipine achieved complete clearance by 6 weeks compared to 77% of patients treated with GTN 0.4% cream for 6 weeks.[13] Given the nonsignificant difference; the authors conclude GTN 0.4% cream is an effective alternative to nifedipine. However, it was noted that patients in the
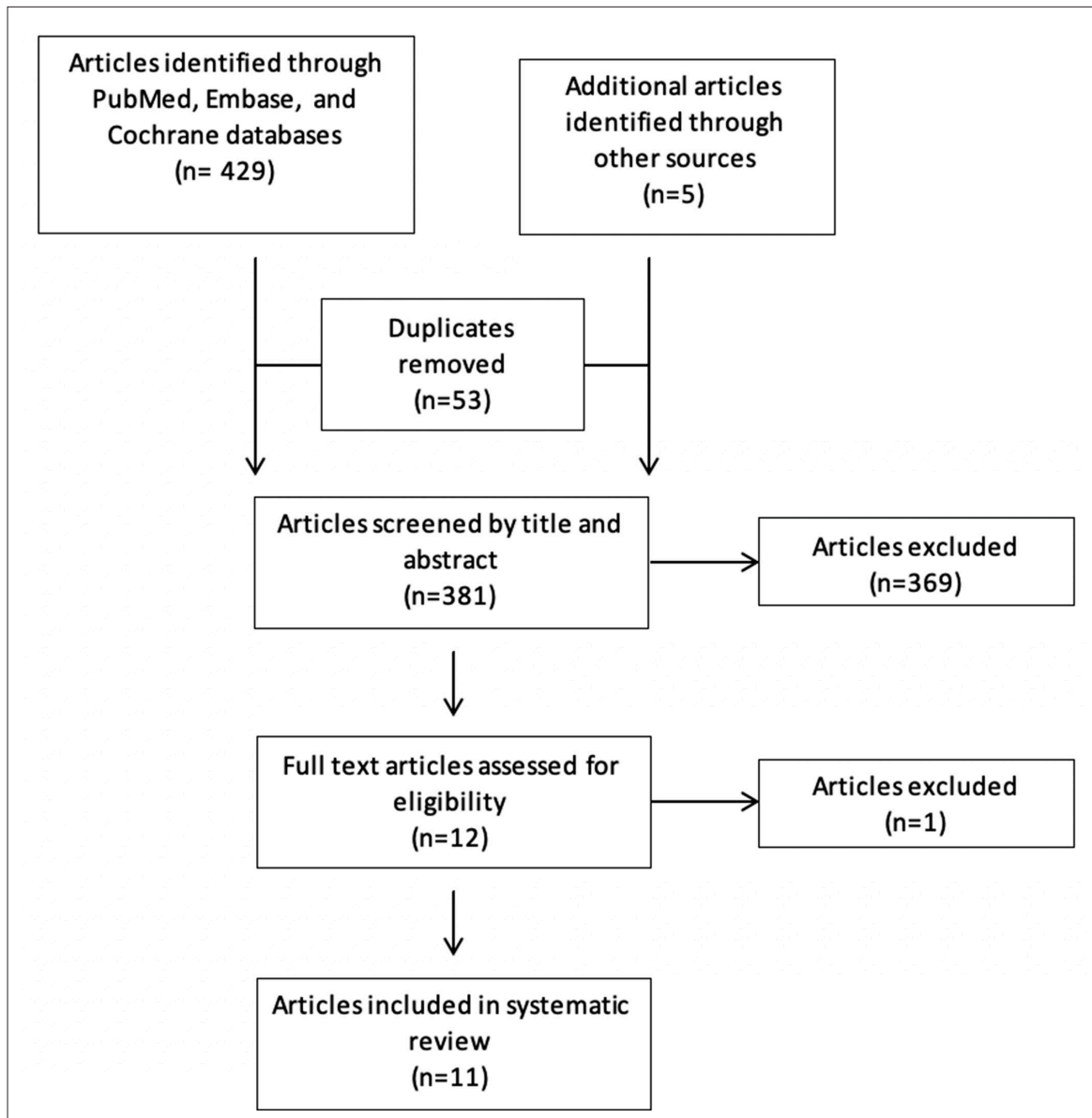
Figure 1. Literature review screening scheme for articles included in our systematic review of chilblains treatments.

nifedipine group achieved earlier clearance compared to those treated with GTN cream (10.9 ± 6 days vs 16.6 ± 11.5 days, $P = .05$). Severe headaches experienced in the nifedipine group caused 5 patients to discontinue treatment.

Souwer et al. demonstrated that both nifedipine and placebo groups showed improvement on VAS scores after 6 weeks of treatment, but the difference between groups was nonsignificant.[14] Similarly, differences in investigator-assessed outcomes were nonsignificant. Calculations were performed with and without correction for ambient temperature, and carry-over effect was reported as negligible. The authors corrected for ambient temperature, a major confounder, by recording the daily ambient temperature

and correcting for temperature changes during the study using a mixed effects model. Nifedipine was associated with significantly lower systolic blood pressure compared to placebo (134.5, 147.1 mm Hg, $P = .02$), and significantly higher peripheral edema score (based on patient reported VASs).

Jain et al. also reported that 10/42 patients (23.8%) in the nifedipine group vs 3/42 patients (7%) in the minoxidil group showed "very good improvement" (complete regression of erythema, edema, vesicles, and ulcer), $P = .001465$.[12] No side effects were experienced in either group.

Table 1. Overview of Study Interventions, Methods, Outcomes, and Limitations for the Articles Included in This Systematic Review of Chilblains Treatments.

Study type (author, year)	Intervention	Control/comparison(s)	n (completed study)	Key findings	Major limitations	Side effects	Oxford Level of Evidence (LOE)	Quality score (U.S. Preventive Services Task Force)
Nifedipine								
Randomized placebo-controlled crossover trial (Dowd, 1986)	Nifedipine retard 20 mg PO TID for 6 weeks	Placebo	10(10)	Positive nifedipine: 7/10 patients (70%) in the nifedipine group, had resolution of lesions within 10 days (vs 20-28 days with placebo), and no new lesions developed while on treatment. Five patients initially treated with placebo relapsed within one week of starting placebo. For 3/5 patients (60%) in the placebo group, code was broken due to relapse severity and nifedipine was restarted with good response	• No correction for ambient temperature. • Not intention-to-treat analysis • exclusion criteria vague ("otherwise well")	Mild dizziness, flushing, and occasional headaches with nifedipine. Only one patient needed a dose reduction due to symptomatic hypotension	Ib	Fair
RCT (Patra, 2003)	Nifedipine (plain) 10 mg PO TID until complete relief and then nifedipine extended release 20 mg PO daily (total duration 21 days)	Diltiazem 60 mg PO TID for 21 days	36(35)	Positive nifedipine: 21/24 patients (88%) in the nifedipine group showed 80% to 90% improvement by the 14th day, vs only 5/12 patients (42%) in the diltiazem group.7/12 (58%) having no response to diltiazem were switched to the nifedipine group between days 7-10	• No correction for ambient temperature. open comparative trial • Cross-over patients were not differentiated from overall outcomes. • Statistical significance was not calculated	One patient developed dizziness and hypotension immediately after nifedipine administration and was excluded from the study	Ib	Fair
RCT (Kubais, 2010)	Nifedipine sustained release 20 mg PO daily for 1 week, followed by 20 mg PO BID for 1 week	Topical 5% minoxidil solution applied twice daily for 2 weeks	62(52)	Positive nifedipine: 20 patients (57%) in the nifedipine group showed good improvement, 9 (25%) very good improvement, compared to 6 patients (35%) with good improvement and 1 patient (6%) with very good in the minoxidil group (P < .05)	• No correction for ambient temperature. • "Single blind" in abstract, but "open comparative" in methods • 73% had below normal BMI • Baseline characteristics unclear	Flushing (54%), constipation (9%), and headache (6%) were reported in the nifedipine group. All normotensive patients maintained controlled blood pressure. No side effects recorded in minoxidil group	2b	Poor

(Continued)

Table 1. Continued

534

Study type (author, year)	Intervention	Control/comparison(s)	n (completed study)	Key findings	Major limitations	Side effects	Oxford Level of Evidence (LOE)	Quality score (U.S. Preventive Services Task Force)
RCT (Khalid, 2014)	Nifedipine retard 10-20 mg PO daily for 1 week, followed by an increase to 20-40 mg PO daily for 5 weeks if tolerated	Topical GTN (0.4%) cream applied twice daily for 6 weeks	65(53)	Positive nifedipine: nifedipine group achieved earlier clearance compared to those treated with GTN cream (10.9 ± 6 days vs 16.6 ± 11.5 days, $P = .05$)	• No correction for ambient temperature • Baseline characteristics unclear	5/26 patients discontinued nifedipine due to severe headache. 1 minoxidil patient reported mild local irritation	Ib	Fair
Randomized placebo-controlled controlled crossover trial (Souwer, 2016)	Nifedipine controlled release (CR) 30 mg PO daily for 2 weeks, followed by nifedipine CR 30 mg PO BID for 4 weeks	Placebo	32(32)	Nonsignificant nifedipine: After 6 weeks of treatment, mean scores on the visual analog scale (VAS) on complaints showed a nonsignificant difference of 1.84 mm in favor of nifedipine ($P = .44$), VAS on disability showed a nonsignificant difference of 0.56 mm in favor of placebo ($P = .75$)	• Lower dose of nifedipine for the first 2 weeks compared to initial study. • Patients had much shorter duration of symptoms compared to initial study (3 weeks vs 5 months yearly for 3 years)	Nifedipine was associated with significantly lower systolic blood pressure and higher incidence of edema	Ib	Good
RCT (Jain, 2018)	Nifedipine 10 mg PO daily and "oral antihistamines" for 2 weeks	Topical 5% minoxidil gel applied twice daily and "oral antihistamines" for 2 weeks	84(84)	Positive Nifedipine: 10/42 patients (23.8%) in the nifedipine group vs 3/42 patients (7%) in the minoxidil group showed very good improvement ($P = .001465$)	• No correction for ambient temperature. • Open comparative trial. • Choice of antihistamine, dose, and frequency not reported	None encountered in either group	Ib	Fair
Pentoxifylline (PTX)								
RCT (Noaimi, 2008)	PTX 400 mg PO TID for 2 weeks	Prednisolone 2.5 mg/kg PO BID and clobetasol ointment for 2 weeks	40(20)	Positive pentoxifylline: prednisolone and clobetasol group 3/11 (27%) who completed treatment had "good improvement," compared to 5/9 (56%) in the pentoxifylline group ($P < .05$)	• No correction for ambient temperature • Baseline characteristics unclear • 50% dropout without explanation • Frequency of clobetasol application not specified	None encountered in either group	2b	Poor
RCT (Noaimi, 2015)	Group B: PTX 400 PO TID for 2 weeks	Group A: Tadalafil 5 mg PO daily for 2 weeks Group C: prednisolone 15 mg PO BID for 2 weeks	58(47)	Tadalafil > PTX > prednisolone: Percentage improvement in severity score was 50.65, 44.16, and 31.51%, for tadalafil, PTX, and prednisolone groups; respectively (ANOVA P value = .004)	• No correction for ambient temperature • Open comparative trial	Mild headache in the first few days in 6 (40%) in tadalafil group but did not necessitate cessation of therapy	Ib	Fair

(Continued)

Table 1. Continued

Study type (author, year)	Intervention	Control/comparison(s)	n (completed study)	Key findings	Major limitations	Side effects	Oxford Level of Evidence (LOE)	Quality score (U.S. Preventive Services Task Force)
RCT (Al-Sudany, 2016)	Pentoxifylline (PTX) 400 mg PO TID for 3 weeks	Placebo	118(110)	Positive pentoxifylline: 40/55 (72.7%) PTX patients achieved very good response at 3 weeks vs 11/55 (20%) placebo patients ($P = .0000000$)	• No correction for ambient temperature. • Baseline characteristics unclear	None encountered in either group	Ib	Fair
Vitamin D and topical corticosteroids								
Randomized placebo-controlled crossover trial (Souwer, 2009)	Vitamin D3 2000 IU PO daily for 7 weeks	Placebo for 3 weeks, followed by vitamin D3 2000 IU PO daily for 4 weeks	37(33)	Nonsignificant Vitamin D: After correction for confounding factors, 19% of subjects reported fewer complaints on VAS, and 6% fewer disability, in both the placebo and vitamin D3 groups		None encountered in either group	Ib	Good
Randomized placebo-controlled crossover trial (Souwer, 2017)	Betamethasone valerate (BMV) 0.1% cream twice daily for 6 weeks	Placebo	34(34)	Nonsignificant BMV: No clinically or statistically significant difference on VAS on complaints (0.56 mm in favor of placebo $P = .744$)		None encountered in either group	Ib	Good

Table 2. Overview of the Inclusion and Exclusion Criteria and the Primary and Secondary Outcomes for the Articles Included in This Systematic Review of Chilblains Treatments.

Study type (author, year)	Inclusion criteria	Exclusion criteria	Primary outcomes	Secondary outcomes
Randomized placebo-controlled crossover trial (Dowd, 1986)	Patients with severe idiopathic perniosis for a minimum of 5 months each year for the previous 3 years	N/A	Changes in clinical appearance, degree of irritation, pain, and soreness	Duration of established lesions and appearance of new lesions
RCT (Patra, 2003)	Patients with perniosis	N/A	• Clinical response to treatment/improvements • Graded into "very good, good, satisfactory, minimal, or no response"	Side effects
RCT (Kubais, 2010)	Patients with perniosis with no previous use of medical remedies	• Pregnant patients • Patients with cardiovascular disease • Children < 12 years • Patients with connective tissue diseases • Patients with Raynaud's phenomenon • Patients on systemic medications such as antiplatelets, aspirin, antiepileptic, and immunosuppressants	• Clinical response to treatment/improvements • Graded into "very good, good, satisfactory, minimal, or no response"	Side effects
RCT (Khalid, 2014)	• Patients with idiopathic perniosis defined as inflammatory lesions (erythema, cyanosis, macules, papules, nodules, or ulcers) involving an acral area (hands, feet or face) associated with itching, pain or tingling sensations along with history of exposure to cold • Male and female patients • Patients who gave written informed consent to participate in the trial	• Patients with systemic diseases • Patients with a history of Raynaud's phenomenon • Patients using topical or systemic medication • Pregnant or lactating patients pregnant or lactating females, Patients < 12 years • Patients > 60 years • Patients with blood pressure below 110/70 mm Hg • Patients with positive ANA or RA factor Exit criteria: • Failure to comply with treatment or follow-up visits • Development of conditions meeting any of the exclusion criteria • Patient's desire to leave the study	• Efficacy of topical vasodilator glyceryl trinitrate (GTN) 0.4% cream, with systemic nifedipine • Lesions treated successfully • Mean time for clearance of lesions	Side effects

(Continued)

Table 2. Continued

Study type (author, year)	Inclusion criteria	Exclusion criteria	Primary outcomes	Secondary outcomes
Randomized placebo-controlled crossover trial (Souwer, 2016)	• Patients with chronic perniosis during the winters of 2010 to 2012 • ages 18 years or older • Patients reported symptoms of perniosis in the past 3 weeks	• Patients with rheumatologic disorders • Patients already using nifedipine or another calcium channel blocker • Pregnant or lactating patients • Contraindications to nifedipine	Visual analog scale on complaints score differences between nifedipine and placebo	Visual analog scale on disability score differences between nifedipine and placebo
RCT (Jain, 2018)	Patients with symptoms and clinical diagnosis of chilblains with no use of previous medical remedies	• Pregnant patients • Patients already using treatments for chilblains	• Degree of severity of chilblains upon treatment • Degree of severity graded to mild, moderate, severe based on new scoring system: "no response, minimal, good, satisfactory, very good"	Side effects
RCT (Noaimi, 2008)	Patients with perniosis with no previous use of medical remedies	• Pregnant patients • Patients with cardiovascular disease • Children < 12 years • Patients with connective tissue diseases • Patients with Raynaud's phenomenon • Patients on systemic medications such as antiplatelets, aspirin, antiepileptic, and immunosuppressants	• Clinical response to treatment/ improvements • Severity scores before and after treatment were calculated using a system proposed by the authors that accounted for "number of fingers/ toes involved, type of lesion (patch, plaque, bullae, ulcer), presence of coldness, cyanosis, and itching"	Side effects
RCT (Noaimi, 2015)	Patients with perniosis with no previous use of medical remedies	• Pregnant patients • Patients with cardiovascular disease • Children < 12 years • Patients with connective tissue diseases • Patients with Raynaud's phenomenon • Patients on systemic medications such as antiplatelets, aspirin, antiepileptic, and immunosuppressants	• Severity of disease before and after treatment • Innovative scoring system was used based on the number of fingers/ toes, type of the lesions and the presence of coldness, cyanosis, or itching	Side effects

Table 2. Continued

Study type (author, year)	Inclusion criteria	Exclusion criteria	Primary outcomes	Secondary outcomes
RCT (Al-Sudany, 2016)	Patients with primary perniosis (chilblains)	• Patients < 15 years • Pregnant and lactating patients • Patients with cardiovascular disorders, history of cerebrovascular accidents, bleeding tendencies • Patients using anticoagulant therapy • Patients allergic to pentoxifylline, or similar medicines such as theophylline or aminophylline • Patients with a connective tissue disorder	• Therapeutic response graded on a 4-point scale • Grade 0: Worse or no response • Grade 1: Minimal response • Grade 2: Satisfactory response • Grade 3: Very good response	Side effects
Randomized placebo-controlled crossover trial (Souwer, 2009)	• Patients aged 16 years or older with chronic chilblains • Reported complaints lasting at least 3 weeks	• Patients with a history of inflammatory disease, urolithiasis, hypercalcemia, hyperparathyroidism • Pregnant or breast-feeding patients • Patients on calcium channel blockers • Patients unable to keep a diary	• Visual analog scale on complaints score differences between nifedipine and placebo • Visual analog scale on disability score differences between nifedipine and placebo	N/A
Randomized placebo-controlled crossover trial (Souwer, 2017)	• Patients ages ≥ 18 years • Patients with complaints of chilblains lasting ≥3 weeks	• Patients with rheumatic disorder • Patients using nifedipine or other calcium antagonist • Patients using a corticosteroid-containing cream in the previous 4 weeks • Pregnant or lactating patients	Visual analog scale on complaints score differences between betamethasone and placebo	Visual analog scale on disability score differences between betamethasone and placebo

Pentoxifylline

There are three studies investigating the treatment of chilblains with pentoxifylline; a placebo controlled RCT,[15] a comparative trial versus combination oral prednisolone and clobetasol ointment,[16] and a comparative trial versus tadalafil and prednisolone.[17]

In 2008, Noaimi et al. conducted an open comparative study (*n* = 40) of oral pentoxifylline 400 mg PO three times vs oral prednisolone 0.5 mg/kg/day plus topical clobetasol ointment for 2 weeks.[16] In the prednisolone and clobetasol group, 3/11 patients who completed treatment had "good

improvement" (symptoms disappeared and symptoms resolved) compared to 5/9 patients in the pentoxifylline group (*P* < .05). It is important to note that only 20/40 (50%) completed the study. No side effects were experienced in either group. Pentoxifylline was shown to be superior to oral and topical corticosteroids.

In 2015, Noaimi et al. further compared pentoxifylline 400 mg PO three times daily, tadalafil 5 mg PO daily, and prednisolone 15 mg PO twice daily for the treatment of idiopathic chilblains over 2 weeks.[17] Percentage improvements after treatment was 50.65%, 44.16%, and 31.51% for

Table 3. Overview of Side Effects and Frequency for the Articles Included in This Systematic Review of Chilblains Treatments.

Study type (author, year)	Frequency and side effects in the intervention group	Frequency and side effects in the control/comparison(s) group
Nifedipine		
Randomized placebo-controlled crossover trial (Dowd, 1986)	• Mild dizziness • Flushing • Occasional headaches • 1/10 patient required reduction of the dose to 40 mg nifedipine due to hypotension	N/a
RCT (Patra, 2003)	Nifedipine 10 mg, 20 mg (n = 25) 1/25 patient complained of dizziness after taking nifedipine; patient was given a capsule of nifedipine under observation, but developed dizziness and hypotension	No side effects
RCT (Kubais, 2010)	Nifedipine 20 mg (n = 42) • 19 patients had flushing • 3 had constipation • 2 patients had headaches	No side effects
RCT (Khalid, 2014)	Nifedipine retard 10-20 mg × 1 week, 20-40 mg × 5 weeks (n = 34) 5/34 patients had severe headaches	Topical GTN (0.4%) × 6 weeks (n = 31) 1/31 patients had mild local irritation
Randomized placebo-controlled crossover trial (Souwer, 2016)	Nifedipine 30 mg × 2 weeks, 30 mg × 4 weeks (n = 15); compared statistically significant differences between nifedipine arm and placebo arm (n = 17) • Mean systolic blood pressure was significantly lower in nifedipine group (95% CI, −24.1 to −2.0 mm Hg; P = .02) • Mean assessed peripheral edema score on the VAS was increased in nifedipine group (95% CI, 1.1-18.1 mm; P = .03) • Headache and dizziness did not differ significantly	N/a
RCT (Jain, 2018)	No side effects	No side effects
Pentoxifylline (PTX)		
RCT (Noaimi, 2008)	No side effects	No Side effects
RCT (Noaimi, 2015)	Tadalafil 5 mg × 2 weeks (n = 19) 6/19 patients had mild headaches in the first few days	No side effects
RCT (Al-Sudany, 2016)	No side effects	No side effects
Vitamin D and topical corticosteroids		
Randomized placebo-controlled crossover trial (Souwer, 2009)	No side effects	No side effects
Randomized placebo-controlled crossover trial (Souwer, 2017)	No side effects	No side effects

tadalafil, pentoxifylline, and prednisolone, respectively (ANOVA *P* value = .004). Mild headache was experienced by 6(40%) of patients in the tadalafil group in the first few days but did not necessitate cessation of therapy. Tadalafil has a superior effect over pentoxifylline, and that the latter is superior to prednisolone.

Al-Sudany et al. also noted improvements in patients treated with 400 mg pentoxifylline within 1 week. On the

21st day, 40/55 (72.7%) patients using pentoxifylline experienced very good response, vs only 11/55 (20%) in the placebo group (P = .0000000).[15] No side effects were encountered in either group.

Other Therapies: Topical Corticosteroids, Vitamin D

Despite topical corticosteroids being prescribed frequently for the treatment of chilblains, the level of evidence is poor, with only the only supporting study being a case series of topical fluocinolone in 1973.[18] In March 2017, Souwer et al. assessed the efficacy of twice daily application of topical betamethasone valerate 0.1% cream for 6 weeks to treat chilblains, but no clinically or statistically significant differences were found when compared to the placebo.[19]

In 2009, Souwer and Lagro-Janssen published a double-blind randomized trial (n = 33) to assess the efficacy of oral vitamin D3 2000 IU daily as a treatment for chilblains.[20] Over an 8-week period, no significant differences in clinical outcomes were found between vitamin D and the placebo group once confounding factors were adjusted.

Discussion

Nifedipine is a dihydropyridine calcium channel blocker that decreases blood pressure primarily through peripheral vasodilation and is thought to alleviate cold-induced vasospasm. A 2017 Cochrane review (38 studies, n = 982 patients), concluded that calcium channel blockers "probably slightly reduce" the frequency, severity, and overall patient assessment of raynaud's attacks.[21] Importantly, while common side effects included headache, dizziness, nausea, palpitations, and ankle edema, there were no serious adverse events experienced by participants in any of these studies. Although the evidence for nifedipine use in the treatment of chilblains is less robust than that for raynaud's, it is still widely prescribed.

Raynaud's phenomenon often presents as cold digits with a demarcated white area known as a white attack. There may be a cyanotic skin change, which is blueish in color known as a blue attack. The attack begins with a single digit which then spreads to other digits symmetrically and bilaterally. The raynaud's attack is due to a transient and peripheral vasoconstrictive response to cold temperatures or emotional stress usually occurring in the digital and cutaneous arteries. This phenomenon has been shown to occur via three mechanisms including decreased blood flow, blood vessels constriction, neurogenic responses, and inflammatory and immune responses.[22]

The transient receptor potential (TRPM8) ion channel is activated by the A-delta and unmyelinated C-fibers, which are activated by cold temperature. The activation for TRPM8 leads to cutaneous vasoconstriction and thermogenesis. Cold temperature also stimulates the release of vasoconstricting neuropeptides and norepinephrine, which leads to decreased blood flow to the skin. In primary raynaud's, there is an increase in alpha-2 adrenergic sensitivity in the digital and cutaneous vessels. This leads vasoconstriction in response to cold temperatures and emotional stress. In secondary raynaud's, there is an underlying condition resulting in the vasoconstriction. Often the endothelial function is impaired leading to vasoconstriction and schema in the area of skin effected.[22]

Although raynaud's may be a differential diagnosis for chilblains, chilblains, in contrast, is an inflammatory condition that results from cold and damp conditions. Patients often present with multiple symmetrical erythrocyanotic lesions (ie, macule, papule, or nodules) most commonly affecting the hands or feet bilaterally. Although majority of cases are idiopathic and acute, secondary chilblain has associations with underlying conditions such as systemic lupus erythematous. This condition occurs more often in women and in patients living in colder climates.[23]

Because of the rarity of chilblain, the pathogenesis is largely unknown. However, associations with vasospasm when exposed to cold and damp climates has been suggested. The most commonly reported histopathological findings include dermal infiltrate with associated edema; however, these findings are nonspecific.[23]

Six of the ten studies included in our review had nifedipine as a treatment group (combined study population, n = 289), including two randomized placebo-controlled trials.[9,14] While the initial RCT in 1986 showed a very positive effect for nifedipine, the 2016 RCT, which corrected for changes in ambient temperature, reported nonsignificant differences compared to placebo. In the remaining studies, nifedipine was found to be superior to topical glyceryl trinitrate cream, minoxidil, and diltiazem. Nifedipine side effects reported in the five trials were like those observed in the raynaud's studies, and no serious adverse events were experienced. Overall nifedipine is a well-tolerated drug, and there is moderate evidence to support its use in the treatment of chilblains.

Pentoxifylline is a xanthine derivative that inhibits phosphodiesterase and increases perfusion through anti-inflammatory, anti-fibrinolytic, and viscosity-lowering effects. It is only FDA approved for intermittent claudication but is frequently used off-label for a variety of dermatologic conditions.[24] Three studies included in our review showed positive efficacy for pentoxifylline in the treatment of chilblains.[15-17] Notably, there was a relatively large scale placebo-controlled RCT (n = 118), where 72.7% of patients in the pentoxifylline group experienced very good response, vs only 20% in the placebo group (P = .0000000).[15] Results were not corrected for ambient temperature, but the authors felt these differences were unlikely to be a major confounding factor since the study was only conducted in January and February, and an equal number of patients were included in both groups for each of the 4 years. No side effects were

encountered. More common side effects of pentoxifylline reported in the literature include GI upset, dizziness, and headache.[24] Further investigations are required, but the results of the 2016 RCT are promising.

The two remaining studies included in our review were high quality placebo-controlled double-blind randomized trials of topical corticosteroids and vitamin D.[19,20] None of these treatments showed superiority compared to placebo.

It is also important to note chilblain-like eruptions in the recent context of COVID-19. According to a systematic review conducted by Conforti et al., vascular lesions associated with COVID-19 were the second most reported in the literature, majority of which were chilblain-like presentations (*n* = 84). Chilblain-like lesions presented commonly in patients with mild COVID-19 diseases courses and in younger populations.[25] A multi-variate logistic regression analysis recently identified chilblain-like eruption as a favorable prognostic factor for COVID-19 and less likely to be associated with severe infections.[26] It is suggested that the pathogenesis might be a protective response against COVID-19.[27] Chilblain, in the context of COVID-19 has also appeared in warm weathers as opposed to the conventional cold and damp weather, suggesting a COVID-19-related etiology.[28]

In conclusion, there is moderate evidence to support the use of nifedipine and pentoxifylline as systemic treatments for idiopathic chilblains. Further studies are needed to better determine efficacy, as well as optimal dosage and duration of treatment. Both nifedipine and pentoxifylline are relatively safe and well-tolerated dugs, but not without side effects, and therefore benefits and risks must be weighed for each patient.

Declaration of Conflicting Interests

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