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What is the Best Way to Treat Patients with Raynaud's Phenomenon and a Tendency towards Hypotension?

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ABSTRACT Episodes of excessive vasospasm are common in patients with Raynaud's phenomenon (RP). Pharmacological treatment may often result in side-effects such as hypotension, leading to discontinuation of treatment. Review of therapeutic interventions with regard to tendency towards hypotension was done in medical databases including PubMed, Scopus, and Medline to summarize the current state of the knowledge. Despite the episodes of blood pressure drops caused by hypotension, calcium channel blockers (CCB) have been widely used in RP as first-line treatment medication. The use of other CCB apart from nifedipine is controversial due to the variety of results in clinical trials. A clinical study comparing the efficacy and tolerability of losartan with nifedipine revealed a significant reduction in RP severity, frequency of episodes, and reported adverse effects. Application of oral sildenafil 100 mg/d as an add-on therapy increased microvascular blood flow in secondary RP, while being well-tolerated and with no withdrawal from the study. Topical vasodilators may be applied as an adjuvant therapy for patients with RP. Clinical studies approved 10% nifedipine cream and 10% nitroglycerine gel as an efficient RP therapy with side-effects comparable with placebo usage. Non-pharmacological interventions, such as cold avoidance, stress management, and smoking cessation are recommended in reducing episodes of RP.
Calcium channel blockers, with a particular emphasis on nifedipine, in combination with non-pharmacological management seem to be the optimal way to treat the patients with a tendency to hypotension.

KEY WORDS: Raynaud's phenomenon, vasospasm, hypotension, symptoms, treatment

INTRODUCTION

A physiological response to cold exposure retains constant body temperature through peripheral vasoconstriction of thermoregulatory precapillary arterioles and arteriovenous anastomoses (1). Raynaud's phenomenon (RP) is characterized by paroxysmal and reversible episodes of excessive vasospasm to triggers such as cold temperatures or emotion (stress), which typically involve distal parts of the body, i.e. the fingers or toes (1,2). In the classic triphasic response, patients report the following color changes on their digits: white (ischemia), blue (hypoxia), and red (reperfusion) (3). Attacks typically last for approximately

Table 1. Comparison of calcium channel blockers in clinical studies

Medication	Author	Year	Study [n]	Dose [mg/d]	Duration	The mean attack rate per duration	Side effects	Withdrawals due to hypotension
Nifedipine	Rodeheffer (8)	1983	15 - 5 primary RP - 10 secondary RP	10 mg x 3/d for 3 days 20mg x 3/d if well tolerated placebo: 1 capsule x 3/d	7 weeks - 2 weeks placebo - 2 weeks treatment - 1 week placebo - 2 weeks treatment	Primary RP: 10.0±2.3 placebo vs 2.6±1.3 with nifedipine Secondary RP: 15.0±4.2 placebo vs 13.1 ± 5.1 with nifedipine The mean decrease in attack rate (P=0.048): - primary RP 7.8±2.3 - secondary RP 3.1±1.7	80% headache, 33% dizziness	No data
Nifedipine	Ettinger (9)	1984	25 - 6 primary RP - 19 secondary RP	20 mg x 3/d placebo: 2 capsules x 3/d	10 weeks - 2 weeks placebo - 2 weeks 1st crossover - 1 week placebo - 2 weeks 2nd crossover - 1 week placebo - 2 weeks 3rd crossover	30.4±4.5 placebo vs 24.7±5.6 with nifedipine	flushing, headache, orthostatic hypotension	3 (primary RP)
Nifedipine	Sarkozi (10)	1986	39 primary RP	10 mg x 3/d for 5 weeks 20 mg x 3/d for 5 weeks if well tolerated	10 weeks	48.2% reduced attacks in the nifedipine group vs 24.6% reduction in the placebo group (P<0.05)	No data	No data
Slow-release nifedipine	Costantini (11)	1987	24 - 16 primary RP - 8 secondary RP	40 mg/d	30 days	Reduction of the ischemic attacks by 88.8% with slow-release nifedipine vs placebo (25.0%)	No data	No data
Slow-release nifedipine	RTS (12)	2000	158 primary RP	30 mg/d for 1 week 60 mg/d if well tolerated	1 year	66% of reduced attacks with slow-release nifedipine vs placebo	24% edema, 17% headache, 8% flushing	No data The incidence of dizziness was slightly lower in the nifedipine group (7%) than in the placebo group (8%).
Isradipine	Leppert (13)	1989	10 Primary Rp	placebo for 3 weeks 1.25 mg x 2/d for 3 weeks 2.5 mg x 2/d for 3 weeks	9 weeks	3 patients had finger vessel closure with placebo vs none with isradipine	No differences placebo vs isradipine	No data
Isradipine	Luca La Civita (14)	1996	33 - 14 Primary RP -19 Secondary RP	5 mg x 1daily for 3 weeks	3 weeks	2.6±1.8 /day with placebo to 1.5±0.9/ day with isradipine	35% flushing 24% headache	No data

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Table 2. Comparison of blood pressure values in 21 patients with RP during therapy with different prazosin dosages (15)

Dosage of prazosin [mg/d]	Blood pressure (mmHg)			
	Supine position		Standing position*	
	Systolic	Diastolic	Systolic	Diastolic
Placebo	123.9 ± 2.4	77.5 ± 2.0	121.8 ± 2.4	77.4 ± 2.2
3 mg/d	120.6 ± 2.4	78.4 ± 2.1	117.5 ± 2.5	77.5 ± 2.1
6 mg/d	118.6 ± 2.2	78.6 ± 2.1	113.1 ± 2.6	77.7 ± 2.1
12 mg/d	115.7 ± 2.9	77.3 ± 2.0	110.0 ± 2.8	75.3 ± 2.4

* After standing upright for 1 minute after 10 minutes supine rest.

10-20 minutes and be accompanied by pain or paresthesia of the digits, which has a strong impact on reducing the quality of life (1,2).

RP can be classified as a primary or a secondary condition. Primary RP is defined as symptoms occurring without any related disorder, whereas secondary RP refers to the presence of an underlying disease, e.g. connective tissue diseases (CTDs) such as systemic sclerosis (SSc) or systemic lupus erythematosus (SLE) (1). More than 90% of patients with SSc experience secondary RP (4). In these cases, vasospasms usually occur and are long-lasting, more frequent, or severe, ultimately progressing to irreversible tissue injuries (3,4). Furthermore, pharmacological treatment often results in adverse effects such as facial flushing, headaches, fluid retention, dizziness, palpitations, and hypotension (1,5). Unexpected blood pressure drops can constitute grounds for treatment withdrawal in view of possible serious complications (5).

METHODS

In this review, we summarize the current evidence for therapeutic options for patients with RP and a tendency towards hypotension during standard RP therapy to improve quality of life. PubMed, Scopus, and Medline databases were searched to review different interventions.

DISCUSSION

Pharmacological approach

Calcium channel blockers (CCB) have been widely used in RP treatment, being the first-line medication of choice (5,6). Despite the improvements in patient condition resulting from CCB, patients with RP sometimes cannot tolerate the side-effects during therapy. Peripheral vasodilation and the consequent drop in blood pressure are commonly accompanied by reflex tachycardia when nifedipine and its analogues are used; this is in contrast to verapamil and diltiazem, whose effects on peripheral vessels are accompanied by cardiodepressant effects (6). The use of other CCB apart from nifedipine (diltiazem, felodipine, amlodipine, nitrendipine, isradipine, or nicardipine) is controversial, due to the variety of results in clinical trials, i.e. their short-term duration. Table 1 compares different studies of CCB in patients with RP, including dosage, duration, effectiveness, and possible impact on hypotension. Therapy with long-acting nifedipine is effective and safe and has also shown a positive response to low temperature changes (6,7).

One of the possible treatment options for RP in patients with a connective tissue disease, including systemic sclerosis (SSc, scleroderma), are alpha-1-adrenergic receptor antagonists (13). A clinical study with different dosages of prazosin (Wollersheim *et al.*, 1988) enrolled 24 patients with RP (14 primary RP, 10 secondary RP). Several measurements including blood pressure values were obtained during follow-up visits, which occurred after every 2-week period of treatment. The decrease in systolic blood pressure after the patients stood upright for 1 minute was more pronounced during the therapy with 12 mg dose of prazosin in comparison with the 3 mg dose, whereas there were no significant differences between the 6 mg and 12 mg daily doses. The majority (75%) of patients found the 6 mg dose more effective than the 3 mg dose. Only three patients reported the 12-mg daily dose of prazosin to be more effective than the 6-mg dose (15).

Another study (Dziadzio *et al.*, 1999) compared the efficacy and tolerability of losartan, an antagonist of angiotensin II receptor type 1, with nifedipine for the treatment of patients with RP. In a randomized, parallel-group, controlled trial, patients with primary RP (n = 25) or RP secondary to SSc (n = 27) were allocated to undergo a 12-week period of treatment with either losartan (50 mg/d) or nifedipine (40 mg/d; 20 mg twice daily). The study revealed a significant mean reduction in RP severity (49%; *P*=0.0003) and frequency of episodes (50%; *P*=0.009) with losartan treatment in comparison with the nifedipine group. Side-effects occurred more often in patients applying nifedipine compared with those taking losartan.

Adverse effects were reported by 39% and 12% of patients receiving nifedipine or losartan, respectively ($P<0.005$). Well-known side-effects such as headache, flushing, nausea, and ankle swelling were reported in the nifedipine group and led to the following withdrawals: 3 patients because of severe headaches and 1 patient because of persistent ankle swelling. Occasional dizziness was reported by 3 out of 26 patients (12%) in the losartan group. The number of patients withdrawing from the study was significantly higher in the nifedipine group (23%) compared with the losartan group (4%; $P<0.02$) (16).

Sildenafil, a phosphodiesterase inhibitor, may be applied as an add-on therapy on the microvascular blood flow in secondary RP to SSc. 41 patients with RP and SSc were randomly assigned to receive oral sildenafil 100 mg/d (n = 21) or placebo (n = 20) for 8 weeks. After 8 weeks of treatment, the sildenafil group presented a significantly higher mean percentage change from baseline in finger blood flow, measured with laser Doppler imaging, before and after cold stimulus ($P=0.026$ and $P=0.028$, respectively) compared with the placebo group. Despite a few reported adverse effects of sildenafil (33% headache, 19% flushing, 9% nausea), the treatment was well-tolerated, with no withdrawal from the study (17).

Topical vasodilators may be applied as an adjuvant therapy for patients with RP. Several trials have shown the benefits of topical nitrates, but there is limited evidence for the efficacy of other topical agents. A clinical study (Wortsman *et al.*, 2018) enrolled a small group of patients with secondary RP (n = 10) who applied 5 g of 10% nifedipine cream on one hand and 5 g of 5% sildenafil cream on the other one. The control group comprised the patients' thumbs, which were without topical administration. 10 patients underwent a high-frequency color Doppler ultrasound examination before and 60 minutes after topical application. Topical sildenafil significantly increased blood flow ($P<0.0083$) and diameter ($P=0.0695$) in contrast to therapy with topical nifedipine, where there was no significant improvement in both parameters. Apart from experiencing sensation of heat with topical nifedipine (n = 5) and a tingling sensation with sildenafil therapy (n = 6), no serious adverse effects were found (18).

Topical nitroglycerin gel alleviates the severity of Raynaud's phenomenon during episode onset. A multicenter, randomized, placebo-controlled study was conducted on group of patients with a clinical diagnosis of primary or secondary RP (n = 219). MQX-503 (10% nitroglycerine in propylene glycol) was applied right before or within 5 minutes of the beginning of an episode of RP with a maximum of 4 applications daily and minimum 2-hour interval for each application. Patients were required to fill out Raynaud's Condition Score (RCS) every day, which is a validated questionnaire consisting of self-assessment of the number and duration of episodes, the associated symptoms such as pain and numbness, and the degree of hand disability. Patients receiving MQX-503 experienced significant improvement of Raynaud's Condition Score of 14.3% ($P<0.001$) compared with 1.3% improvement among patients receiving placebo ($P<0.04$). MQX-503 side-effects were comparable to placebo (4).

Non-pharmacological approach

Non-pharmacological interventions have been demonstrated to be a first-line strategy for all patients with RP (19). Digital arteries and thermoregulation are an integral part of sympathetic control. Low temperatures, emotional stress, addictions (i.e. smoking), or stimulating substances are the main factors triggering the vasoconstriction (1,2,19). Cold avoidance, stress management, and smoking cessation have become a common technique recommended for reducing episodes of RP (19).

A randomized controlled clinical trial enrolled 23 patients (15 with primary RP, 8 with secondary RP) in the 8-week study which compared the efficacy between acupressure and targeted patient education. Frequency of attacks decreased by 6.7 attacks in the acupressure group vs. 7.2 in the education group ($P=0.96$), with a simultaneous reduction in duration to 11.4 minutes and 0.8 minutes, respectively ($P=0.14$). No statistically significant differences were detected between the acupressure and education groups in primary and secondary outcomes ($P>0.05$) (20).

A number of additional and alternative therapies have been tested for RP management, but none have demonstrated effectiveness in well-conducted trials (21).

CONCLUSION

Calcium channel blockers have been demonstrated to be effective as first-line pharmacotherapy and should be titrated to the maximum tolerated dose before combining or switching to other therapeutic agents. Due to common intolerance of side-effects, therapy with long-acting nifedipine appears to be more effective and safer compared with other CCB and provokes the least episodes of hypotension. The application of a non-pharmacological approach constitutes an integral part of first-line treatment. Reducing exposure to triggers that provoke vasoconstriction is one of the most effective intervention strategies in patients with RP.

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