Cochrane Library

Cochrane Database of Systematic Reviews

Prazosin for Raynaud's phenomenon in progressive systemic sclerosis (Review)

Harding SE, Tingey PC, Pope J, Fenlon D, Furst D, Shea B, Silman A, Thompson A, Wells GA

Harding SE, Tingey PC, Pope J, Fenlon D, Furst D, Shea B, Silman A, Thompson A, Wells GA.
Prazosin for Raynaud's phenomenon in progressive systemic sclerosis.
Cochrane Database of Systematic Reviews 1998, Issue 2. Art. No.: CD000956.
DOI: 10.1002/14651858.CD000956.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Prazosin for Raynaud's phenomenon in progressive systemic sclerosis

Sarah E Harding[1], Paul C Tingey[1], Janet Pope[2], D Fenlon[3], Dan Furst[4], Beverley Shea[5], Alan Silman[6], A Thompson[7], George A Wells[8]

[1]Department of Medicine, University of Western Ontario, London, Canada. [2]Dept of Medicine and Epidemiology and Biostatistics, University of Western Ontario, London, Canada. [3]Department of Surgery, London Health Sciences Centre, University of Western Ontario, London, Canada. [4]Virginia Mason Research Center, Seattle, WA 98101, USA. [5]Institute of Population Health, University of Ottawa, Ottawa, Canada. [6]ARC Epidemiology Research Unit, University of Manchester, Manchester, UK. [7]Department of Rheumatology, St Joseph's Health Care, London, Canada. [8]Cardiovascular Research Reference Centre, University of Ottawa Heart Institute, Ottawa, Canada

Contact address: Janet Pope, Dept of Medicine and Epidemiology and Biostatistics, University of Western Ontario, St. Joseph's Health Care, 268 Grosvenor St, London, Ontario, N6A 4V2, Canada. Janet.Pope@sjhc.london.on.ca.

Editorial group: Cochrane Musculoskeletal Group
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.

Citation: Harding SE, Tingey PC, Pope J, Fenlon D, Furst D, Shea B, Silman A, Thompson A, Wells GA. Prazosin for Raynaud's phenomenon in progressive systemic sclerosis. *Cochrane Database of Systematic Reviews* 1998, Issue 2. Art. No.: CD000956. DOI: 10.1002/14651858.CD000956.

ABSTRACT

Background

Scleroderma is a connective tissue disease causing fibrosis and commonly affects the skin and internal organs such as the GI tract, lungs, kidney and heart. Most people with scleroderma also have raynaud's phenomenon (RP). One of the possible treatment options for RP in scleroderma is Prazosin.

Objectives

To determine the effects and toxicity of prazosin versus placebo proposed for the treatment of Raynaud's phenomenon (RP) in scleroderma.

Search methods

We searched the Cochrane Controlled Trials Register, and Medline up to December 1996 using the Cochrane Collaboration search strategy developed by Dickersin et al.(1994). Key words included: Raynaud's or vasospasm, scleroderma or progressive systemic sclerosis or connective tissue disease or autoimmune disease. Current Contents were searched up to and including April 7, 1997. All bibliographies of articles retrieved were searched and key experts in the area were contacted for additional and unpublished data. The initial search strategy included all languages.

Selection criteria

Randomized controlled trials comparing prazosin versus placebo were eligible if they reported clinical outcomes from the start of therapy. Trials with a greater than 35% dropout were excluded. Trials were included if patients with diffuse or limited scleroderma were the subjects. If patients with other connective tissue diseases or primary Raynaud's were included, the trial was used if the data on the scleroderma patients could be extracted from the paper.

Data collection and analysis

All data were abstracted by two independent and trained reviewers (DF, AT), and verified by a third reviewer (JP). Each trial was assessed independently by the same two reviewers for its quality using a validated quality assessment tool (Jadad 1996).

Peto's odds ratios were calculated for all dichotomous outcomes and a weighted mean difference was carried out on all continuous outcomes. Fixed effects and random effects model were used if the data was homogeneous or heterogeneous, respectively.

Main results

Two trials with a total of 40 patients were included. Prazosin has been found in two randomized controlled cross-over trials to be more effective than placebo in the treatment of Raynaud's secondary to scleroderma. However, the positive response is modest and side effects are not rare in those taking prazosin.

Authors' conclusions

Prazosin is modestly effective in the treatment of Raynaud's phenomenon secondary to scleroderma.

PLAIN LANGUAGE SUMMARY

Prazosin for Raynaud's phenomenon in progressive systemic sclerosis

Scleroderma is a connective tissue disease causing fibrosis and commonly affects the skin and internal organs such as the GI tract, lungs, kidney and heart. Most people with scleroderma also have raynaud's phenomenon (RP). RP is defined as vasospasm of arteries or arterioles causing pallor and at least one other colour change upon reperfusion such as cyanosis or redness. Primary RP occurs in the absence of causes such as connective tissue disease. Secondary RP occurs in people with underlying diseases that affect blood vessels especially scleroderma and lupus. The RP that occurs in scleroderma is often more severe in that there is not only vasospasm but also a fixed blood vessel deficit with intimal proliferation and therefore narrowing of the blood vessels. Raynaud's phenomenon may also be accompanied by digital ulcers which are possibly secondary to ischemia.

One of the possible treatment options for RP in scleroderma is Prazosin.

Two trials with a total of 40 patients were included. Prazosin has been found in two randomized controlled cross-over trials to be more effective than placebo in the treatment of Raynaud's secondary to scleroderma. However, the positive response is modest and side effects are not rare in those taking prazosin.

BACKGROUND

Scleroderma is a connective tissue disease causing fibrosis and commonly affects the skin and internal organs such as the GI tract, lungs, kidney and heart (Medsger 1985). Most people with scleroderma also have raynaud's phenomenon (RP). RP is defined as vasospasm of arteries or arterioles causing pallor and at least one other colour change upon reperfusion such as cyanosis or redness. Primary RP occurs in the absence of causes such as connective tissue disease. Secondary RP occurs in people with underlying diseases that affect blood vessels especially scleroderma and lupus. The RP that occurs in scleroderma is often more severe in that there is not only vasospasm but also a fixed blood vessel deficit with intimal proliferation and therefore narrowing of the blood vessels. Raynaud's phenomenon may also be accompanied by digital ulcers which are possibly secondary to ischemia.

There have been many randomized controlled trials of both the treatment of idiopathic or primary RP and secondary RP accompanied by scleroderma and other connective tissue diseases. Over the last two decades better drugs have been developed such as calcium channel blockers, prostacyclin analogues and various other medications as opposed to treatment years ago where the choices were ganglion blockers and alpha blockers, both of which had many side effects such as postural hypotension and dry mouth.

These newer drugs seem to be effective and in general are better tolerated than the former medications used to treat RP. There may still, however be a role for older drugs in some patients with recalcitrant RP. However, it has been our impression that RP that is secondary to scleroderma is not as easily treated as idiopathic RP and it is likely due to the fact that there is underlying obstruction of flow in the blood vessels.

We therefore undertook a meta-analysis to determine the efficacy of Prazosin for the treatment of RP in scleroderma.

OBJECTIVES

The objectives of this review were to determine the effectiveness and toxicity of the following agent: Prazosin vs. Placebo proposed for the treatment of RP in scleroderma.

The specific hypotheses tested were that active treatment with Prazosin can:

1) reduce the frequency of attacks

2) reduce the severity of attacks

3) increase digital skin temperature

4) improve the patient and physician's global assessment of the impact of RP

5) prevent new ulcers/gangrene/heal existing ulcers

METHODS

Criteria for considering studies for this review

Types of studies

We aimed to identify all randomized controlled trials (RCTs) in which Prazosin was compared to placebo for the treatment of RP in progressive Systemic Sclerosis.

Types of participants

1) The subjects for the trials should have scleroderma as defined by the physician. It was not necessary that such patients satisfy the preliminary American College of Rheumatology (ACR) criteria for scleroderma (ACR criteria 1980). Trials could include subjects with any subset of scleroderma and at any stage of disease.

2) In the absence of an accepted definition for RP, all subjects reported to have RP were accepted, but the diagnostic criteria used to define RP (e.g. biphasic, triphasic, colour changes of digits) was noted as well as the absence of diagnostic criteria.

Mixed Trials: Some trials included RP patients with a number of different diagnoses. Such trials were included if a subset of patients with scleroderma could be separately identified and their outcome independently assessed.

Design Aspects: Trials must have been truly randomized but, given the nature of some interventions (e.g. infusions), blinding may not have been achieved. Observer and/or subject blindness was noted. Trials with a dropout rate greater than 35% were excluded. Both parallel and crossover trials were included.

Types of interventions

Intervention of interest was Prazosin versus Placebo.

Types of outcome measures

Outcomes were considered for trials of any duration, apart from very short duration (<1 week). They included:

1. Frequency of attacks

2. Severity of attacks

3. Change in digital skin temperature

4. The patient and physician's global assessment of the impact of RP

5. Presence, absence and healing of ulcers or gangrene

Search methods for identification of studies

The aim was to ascertain all trials since 1966 in all languages using the Cochrane search strategy developed by Dickersin et al. (Dickersin 1994). Primary data sources include MEDLINE, Current Contents and the Cochrane Controlled Trials Register (CCTR). Those comparing Prazosin versus Placebo were retrieved from all articles retrieved.

Along with the Dickersin et al (1994) search strategy, the search strategy developed for the Cochrane Musculoskeletal Group (see review group module) was carried out including the following key words:

1. Raynauds or Vasospasm

2 . Scleroderma or Progressive Systemic Sclerosis or Connective Tissue disease or Autoimmune Disease.

Data collection and analysis

All data were abstracted by two independent and trained reviewers (DF, AT), and verified by a third reviewer (JP). Each trial was assessed independently by the same two reviewers for its quality using a validated quality assessment tool (Jadad 1996).

Abstracts, and articles in languages other than English have been collected and will be translated and reviewed for future updates.

A fixed effects model approach will be used to calculate a weighted estimate appropriate for continuous variables and an odds ratio (Peto) for dichotomous variables (Petitti 1994). A random effects model will be used where heterogeneity exists amongst trials. Heterogeneity was tested using a chi square test.

Trials were only included if they were randomized and if the dropout rate did not exceed 35%. The reason for the latter criterion is the fact that the placebo response in RP trials is quite high and therefore results would be biased to the positive if the dropout rate was high as many people would drop out due to non-response. Trials that included patients with scleroderma and other causes of RP such as primary or other secondary connective tissue diseases were included if the data were separated so that the scleroderma patients could be determined. We also decided that if a trial contained at least 80% of patients with scleroderma, and the data were not separated, that trial would still be acceptable. Patients with both diffuse and limited scleroderma were included in the trials and the diagnosis was usually confirmed by the authors' diagnosis of scleroderma. Often the American College of Rheumatology preliminary criteria for the diagnosis of scleroderma were not mentioned.

RESULTS

Description of studies

Two randomized controlled trials of Prazosin versus Placebo were found and included in this meta-analysis. No trials were excluded. Both trials were double blinded and used a cross-over design. In one study (Russell 1985) the duration was two weeks on one treatment (Prazosin or Placebo) with a two week washout and then a final two week on the alternate treatment in random order. The second study (Surwit 1984) employed eight weeks of one treatment and then cross-over for four weeks on the other treatment, with no washout. In the first study the dose of Prazosin was 4 mg per day and in the Surwit study the dose of Prazosin was 3 mg per day. These doses are likely comparable. The outcome measures varied between the two trials but both included a record of RP symptoms and/or the number of vasospastic attacks.

Risk of bias in included studies

The quality assessment was carried out independently by two reviewers (DF, AT).

Using a validated quality assessment tool, we assessed quality defined as "the confidence that the trial design, conduct, and analysis have minimized or avoided biases in its treatment comparisons" (Jadad 1996). The scale consists of items pertaining to descriptions of randomization , double blinding, dropouts and withdrawals as described in the report of the trial, and, in addition, consensus was reached on all final scores for each trial. Interobserver agreement was measured using kappa values (> 0.60 indicate substantial strength of agreement) (Cohen 1988).

The quality of the studies were as follows:

Russell 1985 = 4
Surwit 1984 = 3

Effects of interventions

Two trials met the inclusion criteria. No trials were excluded. Not all outcomes of interest were reported. In both trials Prazosin was favoured over placebo. In the Surwit (1984) study, the frequency of attacks was reduced in the active treatment group; WMD -3.50 [95% CI -5.85, -1.15]. In the Russell (1985) study the percent improvement was poor in both groups with 1 out of 5 improving in the experimental treatment and 0 out of 5 in the placebo group. Side effects were only reported by Surwit (1984) and they occurred only for those taking Prazosin, 2 out of 11 in the experimental group vs. 0/9 in the placebo group [OR 6.82 (95% CI 0.39, 119.27)].

DISCUSSION

RP is extremely common in scleroderma and often severe. The literature search for this meta-analysis reveals that many different classes of drugs have been demonstrated to have some degree of efficacy in the treatment of RP with respect to decreasing RP frequency and severity, and preventing or healing digital ulcers. Because RP is variable and many patients are entered into studies such as these when they are having frequent and severe attacks, there is a high placebo response because of the variability of RP with respect to temperature and other emotional factors. Regression to the mean may occur, therefore explaining the relatively high placebo response in most trials. This placebo response should be taken into consideration when other drugs are compared (both in primary and secondary RP) and therefore any new drugs studied should be blinded and the trial should have a control group.

Two articles were found for this analysis and both were included. It is important to note the subject numbers were quite small.

There are several limitations to the meta-analysis. Our search from MEDLINE and the references of key review articles may only reveal some of the published articles. Therefore, at this point in time some articles could be missing. However we have already demonstrated efficacy with Prazosin, so additional positive articles may confirm these results but not dramatically change them. There may also have been publication bias where a negative study is less likely to be published. However it is our clinical impression as well as agreeing with the results of these trials that many drugs are effective in the short-term treatment of RP. Therefore, some negative studies would need to exist to negate the positive trial results.

Many outcome measurements were different in each trial so a direct comparison was not easy. However, we have tried to compare the outcome measurements in a common fashion.

We were unable to find results on all our outcomes of interest, as the data were not given for some, and the outcomes we selected were not part of the outcomes used in the trials. The two studies differed

in Prazosin dose and study duration, which make them even less comparable.

This meta-analysis does not address side effects except for the fact that if a trial had more than 35% of its' participants drop out, then it was not included and in those latter trials the side effects certainly could have been worse. In one trial (Russell 1985) subjects with scleroderma and other causes of RP were included and the side effect profile was not stratified with respect to the scleroderma patients compared to other patients. Many of the authors commented that the response in scleroderma with respect to the RP was sub-optimal compared to those with idiopathic RP. For the various reasons mentioned earlier this makes sense that the scope of this meta-analysis was not to compare the efficacy of treatment of RP in scleroderma versus other conditions so this was not addressed in this review. With the presentation of changes from baseline and variance or a standard deviation provided for each trial, it will allow future researchers to calculate sample sizes for new drugs that may be used in the treatment of RP scleroderma.

The dose of Prazosin, the duration of treatment and the absence of a washout period in one trial as compared to the other all make it difficult to compare these two trials. However, given these limitations, it appears that Prazosin is more effective than placebo in controlling RP which is secondary to scleroderma but the results are only modest at best.

AUTHORS' CONCLUSIONS

Implications for practice

Prazosin has been found in two randomized controlled cross-over trials to be more effective than placebo in the treatment of RP secondary to scleroderma. However, the positive response is modest and side effects are not rare in those taking Prazosin.

Implications for research

It certainly can be noted that the treatment of RP which is secondary to connective tissue disease such as scleroderma, is in general more difficult than the treatment of idiopathic RP probably due to the enhanced severity of patients having RP due to scleroderma. Many trials also show a very high placebo response rate in RP whether it is idiopathic or secondary to a connective tissue disease and this is important for sample size calculations if further drugs are studied. Interestingly the placebo response in both of these trials however was not high. It is also difficult to determine an adequate trial duration in a RP trial as it is important that cross-over design does not change seasons such as winter to late spring as ambient temperature certainly can influence the frequency and severity of RP attacks.

REFERENCES

References to studies included in this review

Russell 1985 *{published data only}*

Russell IJ, Lessard JA. Prazosin treatment of Raynaud's phenomenon: a double blind single crossover study. *Journal of Rheumatology* 1985;**12**(1):94-8.

Surwit 1984 *{published data only}*

Surwit RS, Gilgor RS. Allen LM.Duvic M. A double-blind study of prazosin in the treatment of Raynaud's phenomenon in scleroderma. *Archives of Dermatology* 1984;**120**(3):329-31.

Additional references

ACR criteria 1980

ARA Preliminary criteria for the classification of systemic sclerosis (scleroderma): special article. *Arthritis and Rheumatism* 1980;**23**:581-90.

Cohen 1988

Cohen J. Statistical Power Analysis for the Behavioural Sciences. 2nd Edition. Hillside, New Jersey: Lawrence Erlbaum Associates Inc, 1988:21-34.

Freedman 1984

Freedman RR, Ianni P. Wenig P. Behavioral treatment of Raynaud's phenomenon in scleroderma. *Journal of Behavioral Medicine* 1984;**7**(4):343-53.

Freedman 1989

Freedman RR, MD. Induction of vasospastic attacks despite digital nerve block in Raynaud's disease and phenomenon. *Circulation* 1989;**80**(4):859-62.

Hansteen 1976

Hansteen V. Medical treatment in Raynaud's disease. *Acta Chirurgica Scandinavica. Supplementum* 1976;**465**:87-91.

Jadad 1996

Jadad A, Moore A, Carrol D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**:1-12.

Kahaleh 1994

Kahaleh MB. Raynaud's phenomenon and vascular disease in scleroderma. *Current Opinion in Rheumatology* 1994;**6**:621-7.

LeRoy 1992

LeRoy EC, Medsger TA. Raynaud's Phenomenon: A Prosposal for Classification. *Clinical and Experimental Rheumatology* 1992;**10**:485-8.

Medsger 1985

Medsger TA JR. Systemic sclerosis (scleroderma), eosinophilic fascitis, and calcinosis. In: McCarty DJ editor(s). Arthritis and Allied Conditions. 10th Edition. Philadelphia: Lea and Febiger, 1985:944-1036.

O'Brien 1992

O'Brien BM, Kumar PAV, Mellow CG, Oliver TV. Radical Microarteriolysis in the Treatment of Vasospastic Disorders of the Hand, Especially Scleroderma. *Journal of Hand Surgery* 1992;**17B**:447-52.

Petitti 1994

Petitti D. Meta-analysis, decision analysis, and cost-effectiveness analysis: methods for quantitative synthesis in medicine. New York: Oxford University Press, 1994:90-114.

Surwitt 1983

Surwit RS, Gilgor RS, Duvic M, Allen, LM, Neal JA. Intra-arterial reserpine for Raynaud's syndrome. Systemic reactions without therapeutic benefit. *Archives of Dermatology* 1983;**119**(9):733-5.

Wise 1994

Wise RA, Wigley F. Acute effects of misoprostol on digital circulation in patients with Raynaud's phenomenon. *Journal of Rheumatology* 1994;**21**(1):80-3.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Russell 1985

Methods	A randomized placebo-controlled clinical trial Crossover design. Double Blind Efficacy
Participants	N=20, (16 females and 4 males, median age = 50 years) --6 of 20 had progressive systemic sclerosis --5 of these 6 pts completed the study. Pts with symptomatic Raynaud's Phenomenon with recurrent vasospastic episodes--all pts were ambulatory outpatients. Country: USA

Russell 1985 *(Continued)*

Interventions	Study divided into 3 sequential 2-week periods. 1st 2 weeks, pts took one of 2 coded meds (prazosin or identical placebo) then had a 2 week washout period , then were crossed over to the other preparation for the last 2 weeks. Prazosin 1mg qhs on day 0, and 1 mg BID on days 1, 2, 3, and 1 mg qam and 2 mg qhs on days 4, 5, 6, and 2 mg BID for days 7 through 13, and 2 mg in am of day 14 prior to return visit. Duration: 6 weeks
Outcomes	Plethysmographic digital blood flow measurements with cold challenge. Blood samples on last day of tx with q preparation (prazosin levels). Daily record /diary of symtoms during 4 weeks of coded drug ingestion --2 page questionnaire
Notes	Quality Score=4.

Surwit 1984

Methods	A randomized placebo-controlled clinical trial Cross over design Double blind Efficacy
Participants	N=20 with PSS, 18 females and 2 males Source of Population: Community Country: USA
Interventions	Subjects matched in pairs on basis of average skin temp of their middle fingers One week baseline run-in period Either prazosin 1mg TID increased at 4 weeks to 2 to3 mg TID or matching placebo for 8 weeks At week 8 the subjects crossed over for 4 weeks only.
Outcomes	Daily # of vasospastic attacks Average weekly frequency and severity of vasospastic attacks for the 12 week period Duration: 13 weeks
Notes	Quality Score: 3

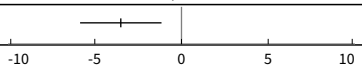
DATA AND ANALYSES

Comparison 1. Prazosin vs. Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 frequency of attacks	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 % improvement	1	10	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]
3 side effects	1	20	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.82 [0.39, 119.26]

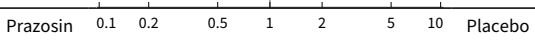
Analysis 1.1. Comparison 1 Prazosin vs. Placebo, Outcome 1 frequency of attacks.

Study or subgroup	Control N	Control Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Surwit 1984	11	-4.9 (3.3)	9	-1.4 (2)		0%	-3.5[-5.85,-1.15]



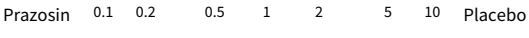
Analysis 1.2. Comparison 1 Prazosin vs. Placebo, Outcome 2 % improvement.

Study or subgroup	Control n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Russell 1985	1/5	0/5		100%	7.39[0.15,372.38]
Total (95% CI)	**5**	**5**		**100%**	**7.39[0.15,372.38]**
Total events: 1 (Control), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1(P=0.32)					



Analysis 1.3. Comparison 1 Prazosin vs. Placebo, Outcome 3 side effects.

Study or subgroup	Control n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Surwit 1984	2/11	0/9		100%	6.82[0.39,119.26]
Total (95% CI)	**11**	**9**		**100%**	**6.82[0.39,119.26]**
Total events: 2 (Control), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.31(P=0.19)					



WHAT'S NEW

Date	Event	Description
3 September 2008	Amended	Converted to new review format. CMSG ID: C070-R

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- University of Western Ontario, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic alpha-Antagonists [*therapeutic use]; Prazosin [*therapeutic use]; Raynaud Disease [*drug therapy] [*etiology]; Scleroderma, Systemic [*complications]

MeSH check words

Humans