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[Intervention Review]

Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis

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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.

Objectives

To assess the effects and toxicity of the following agents:Prostaglandin analogues together with other agents proposed for the treatment of Raynaud's phenomenon (RP) in scleroderma.

Search methods

We searched the Cochrane Controlled Trials Register, and MEDLINE up to 1996 using the Cochrane Collaboration search strategy developed by Dickersin 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 All bibliographies of articles retrieved were searched and key experts in the area were contacted for additional and unpublished data.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

All randomized controlled trials comparing prostaglandin analogues versus placebo were eligible if they reported clinical outcomes within the start of therapy, and if the dropout rate was less than 35%.

Data collection and analysis

Data were abstracted independently by two reviewers (DF, AT). Peto's odds ratios were calculated for all dichotomous outcomes and a weighted mean difference was calculated for all continuous outcomes. A fixed effects or random effects model was used if the data were homogeneous or heterogeneous, respectively.

Main results

Seven randomized trials and 332 patients were included. Five of the seven trials were of parallel design. Five trials compared I.V. Iloprost and one trial studied p.o. Iloprost and another p.o. Cisaprost. Some trials were dose finding trials so various doses of Iloprost were used. Due

to different efficacies of I.V. Iloprost, oral Iloprost and oral Cisaprost, the overall efficacy of these drugs was somewhat diluted. Intravenous Iloprost appears to be effective in the treatment of secondary Raynaud's phenomenon.

Authors' conclusions

Intravenous Iloprost is effective in the treatment of Raynaud's phenomenon secondary to scleroderma at decreasing the frequency and severity of attacks and preventing or healing digital ulcers. The effect seems to be prolonged after the intravenous infusion is given. Oral Iloprost may have less efficacy than intravenous Iloprost. However, Cisaprost has minimal or no efficacy when given orally for the treatment of Raynaud's phenomenon secondary to scleroderma.

PLAIN LANGUAGE SUMMARY

Iloprost and cisaprost 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.

Seven randomized trials and 332 patients were included. Five of the seven trials were of parallel design. Five trials compared I.V. Iloprost and one trial studied p.o. Iloprost and another p.o. Cisaprost. Some trials were dose finding trials so various doses of Iloprost were used. Due to different efficacies of I.V. Iloprost, oral Iloprost and oral Cisaprost, the overall efficacy of these drugs was somewhat diluted. Intravenous Iloprost appears to be effective in the treatment of secondary Raynaud's phenomenon.

Intravenous Iloprost is effective in the treatment of Raynaud's phenomenon secondary to scleroderma at decreasing the frequency and severity of attacks and preventing or healing digital ulcers. The effect seems to be prolonged after the intravenous infusion is given. Oral Iloprost may have less efficacy than intravenous Iloprost. However, Cisaprost has minimal or no efficacy when given orally for the treatment of Raynaud's phenomenon secondary to scleroderma.

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 pallour 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. RP 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 Raynaud's phenomenon. It seems 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. Therefore, new drugs have been studied in subjects with moderate to severe RP secondary to Scleroderma including Iloprost and Cisaprost.

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

OBJECTIVES

The objectives of this review were to determine the effectiveness and toxicity of the following agents: Iloprost and Cisaprost versus Placebo proposed for the treatment of RP in scleroderma.

The specific hypotheses tested were that Iloprost and Cisaprost 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 or 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 one of the above agents was compared either to placebo or to one of the other agents in the group.

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. Trials could include subjects with any subset of scleroderma and at any stage of disease (1980).

2) Definition of Raynaud's Phenomenon:
In the absence of an accepted definition for RP, all subjects reported to have RP were accepted, but the diagnostic criteria used for RP or the absence of diagnostic criteria were noted for each study.

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 or subject blindness was noted. Trials with a dropout rate of greater than 35% were excluded. Both parallel and crossover trials were included.

Types of interventions

Interventions of interest were Prostaglandin analogues, i.e.., Iloprost and Cisaprost versus Placebo.

Types of outcome measures

Outcomes were considered for trials of greater than two days duration. Outcome measures included:

1. Frequency of attacks

2. Severity of attacks

3. Digital skin temperature

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

5. Digital ulcers

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 1994. Primary data sources include MEDLINE, Current Contents, and the Cochrane Controlled Trials Register (CCTR).

Along with the Dickersin 1994 search strategy, the search strategy developed for the Cochrane Musculoskeletal Group 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 using a predeveloped form, 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 was 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 RP, or other secondary connective tissue diseases were included if the data were separated so that the results from the scleroderma patients could be identified. We also decided that if a trial contained at least 80% of patients with scleroderma, and the data were not separated, that the 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. Often the American College of Rheumatology ARA 1980 preliminary criteria for the diagnosis of scleroderma were not mentioned.

RESULTS

Description of studies

Seven randomized controlled trials were included for this meta-analysis. Trial quality was adequate ranging from a score of 3 to 5 (see included tables for details). Four trials contained only patients with scleroderma and the other three had patients with severe RP of which the scleroderma subjects had extractable data. One study was with oral Iloprost, another with oral Cisaprost and the remainder were of I.V. Iloprost. The duration was highly variable ranging from an evaluation after the third day of treatment, to 10 days after the initiation of treatment, to several weeks after Iloprost was administered. Five of the seven studies were of parallel design. Some of the studies appeared to be Phase Two clinical trials with a dose finding schedule, such as ones where placebo was compared to low dose Cisaprost and high dose Cisaprost over 10 days (Lau 1993).

Risk of bias in included studies

The quality assessment was carried out independently by the 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 tool consists of items pertaining to descriptions of randomization , double blinding, dropouts and withdrawals as described in the report of a RCT. Consensus with respect to quality 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). All quality scores had high kappa values.

Effects of interventions

The overall results do not demonstrate impressive efficacy of Iloprost or Cisaprost. In most studies the placebo group response was very high, and the results in the active treatment group did not reach statistical significance. The Weighted Mean Difference (WMD) of sign and symptom Likert scores hovered at a mean weighted difference of 0. Average duration of attacks had a large confidence interval but still approached 0 on WMD and the severity score slightly favoured active treatment but was close to 0.

When examining Iloprost versus placebo, the number of patients improved in the Belch 1995 study yielded an odds ratio of 2.55 [95% CI 0.96,6.80] which bordered on statistical significance. The number of digital ulcers healed was highly significant in the Iloprost group in the Wigley 1992 study. Side effects were also more common in all studies in the Iloprost patients compared to the placebo subjects. Physician global assessment (with respect to number of subjects improved) was statistically significant with an odds ratio of 2.61[95% CI 1.27, 5.38] from the Wigley 1994 study. Therefore, both improvement and side effects were more common in Iloprost compared to placebo. In Cisaprost versus placebo no results were statistically significant at the p <0.05. The trend was for minimal improvement in Cisaprost compared to placebo. When assessing the WMD in Iloprost versus placebo for a sign and symptom change on a Likert scale, no differences were found and average duration of attacks also yielded no differences between Iloprost and placebo.

In Iloprost versus placebo trials the change from baseline severity, yielded a WMD of -0.69 [95% CI -1.117, -0.257]) which was statistically significant <0.05. Therefore, this favoured Iloprost treatment, but the effect was only very small overall.

The frequency of attacks in Iloprost versus placebo favoured Iloprost but did not at all approach statistical significance with a WMD of -0.80 [95% CI -4.71, 3.11].

Due to the seemingly different effects of p.o. Iloprost compared to I.V. Iloprost, an analysis of I.V. Iloprost was performed. The results in these trials revealed that I.V. Iloprost seems very effective and oral Iloprost and Cisaprost appear to be much less effective. The duration of the trials was highly variable and these drugs may decrease RP even several weeks or months after their administration especially with I.V. Iloprost. Possibly due to variable doses, different lengths of follow up, and a high placebo response, it is difficult to find strongly positive results for RP in scleroderma treated by Iloprost and Cisaprost.

DISCUSSION

Raynaud's Phenomenon 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 and 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 which may be from regression to the mean. This placebo response should be taken into consideration when other drugs are considered for experimentation in both primary and secondary RP and therefore any new drugs studied should be blinded and the trial should have a control group.

Fifteen studies were initially found for this meta-analysis. One trial did not have participants with RP secondary to scleroderma. Two other studies had no control group and therefore were excluded. Twelve trials studied subjects with scleroderma of which seven were included. The five trials that were excluded did not give a subset analysis for patients with RP secondary to scleroderma. These trials included subjects with primary and secondary RP. The authors have been contacted to try to obtain the raw data in these trials. It is difficult to directly compare relative efficacy of Iloprost compared to Cisaprost as the effect size is different in the two drugs.

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 some efficacy in RP with Iloprost, 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 Raynaud's phenomenon. Therefore, large numbers of 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. For instance, frequency and severity of attacks could be recorded over one week in one trial or two weeks in another. The severity of RP was recorded by various scales such as Likert scales ranging from 0-4 in one trial and perhaps using a 10 cm visual analog scale in another trial. However, we have tried to compare the outcome measurements in a common fashion. The length of follow up varied, and if Iloprost or Cisaprost have a delayed onset of action, then short trials (such as three days of treatment) may be falsely negative even if the effect is helpful later on.

We were unable to record temperature as one of our a priori outcome measurements from these trials for two reasons: 1) Temperature was not mentioned in many of the trials, and 2) The digital temperature was recorded quite differently in the trials where it was used and the ambient temperature, the season and the phase of the patient's RP attack would change these results. Therefore, we thought that this was not a clinically helpful outcome measurement.

This meta-analysis does not address side effects. However, trials with more than a 35% drop out rate were not included. In longer trials with large amounts of subjects not completing active treatment, the side effects certainly could have been worse. In most trials where the patients enrolled in the study had scleroderma and other diseases or idiopathic RP, the side effect profile was not usually stratified with respect to the scleroderma patients, so qualitative side effect profiles were unavailable. 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 it 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 the data presented.

With the presentation of changes from baseline and variance or a standard deviation provided for each trial, this meta-analysis will allow future researchers to calculate sample sizes for new drugs that may be used in the treatment of RP in patients with scleroderma.

AUTHORS' CONCLUSIONS

Implications for practice

I.V. Iloprost may be very effective in the treatment of severe RP from scleroderma and can decrease the frequency and severity of RP and in some cases, increase digital ulcer healing.

Implications for research

A placebo group is imperative in studies looking at RP from scleroderma due to the observation that the placebo response is often very high. There may be regression to the mean (whereby just being in a trial after having severe RP, the attacks can decrease in frequency and severity once a patient has entered into a study even if placebo is administered). From these trials, sample size calculations can be shown to need large numbers of subjects if Iloprost will be compared in future to another active treatment. It is also helpful for researchers to include the baseline characteristics of the population studied such as mild, moderate or severe RP and to try to obtain a standardized definition of both the diagnosis of scleroderma and the description of Raynaud's Phenomenon.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

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

Belch 1995

Methods	A randomized multicenter double-blind placebo-controlled clinical trial Efficacy Parallel design
Participants	N=63, 58 female and 5 male with PSS Source of Population: Community of Dundee, Glasgow, and London Country: Britain
Interventions	2 week washout period on no medications Either oral Iloprost 50 ug BID for first day, then 100ug BID for 2nd day, then 150ug BID on 3rd day or to max tolerable dose or placebo for ten days.
Outcomes	Diary cards for duration, severity, and pain of RP attacks Formal assessment of bp, pulse and condition at start of 10 day treatment period, day 3, day 10, and 2 weeks after cessation. Routine haematology and biochemistry blood work on day 0 and day 10 Duration: 38 days
Notes	Quality Score: 5

Kyle 1992

Methods	A randomized controlled trial Double blind Efficacy Parallel design
Participants	Thirteen patients with Raynaud's phenomenon severe enough to warrant admission to hospital for IV Source of population: Hospital Country: UK Mean age: 44 yrs.
Interventions	Iloprost 6 h infusions on 3 consecutive days Placebo
Outcomes	Diary cards were used to report: Frequency of attacks Duration of attacks Severity of attacks Thermographic assessments of digital temperature

Kyle 1992 *(Continued)*

Notes	Quality Score: 3

Lau 1993

Methods	A randomized placebo-controlled clinical trial multicentre: 3-centres Double-blind Efficacy Parallel design
Participants	N=49 with PSS Source of Population: Outpatient clinics Country: Scotland and England
Interventions	7 day run-in period with no meds Randomized to either placebo or Cisaprost 2.5 ug TID or Cisaprost 5ug TID for 10 days
Outcomes	Frequency and duration of RP attacks using a diary card Above recorded in the 7 day run-in period and each day of the 10 day study Patients were assessed at 2 weeks and 4 weeks after study completion Duration: 45 days
Notes	Quality Score: 3

McHugh 1988

Methods	A randomized controlled trial Double blind Efficacy Cross over study
Participants	Twenty nine patients with severe Raynaud's phenomenon, all suffering at least 12 attacks per week Source of population: Community Country: UK Mean age: 56.6
Interventions	Iloprost 2.0 ng/kg/min Placebo
Outcomes	Number of attacks per week Duration Severity Pain Side effects
Notes	Quality Score: 3

Wigley 1992

Methods	A double blind placebo controlled parallel study (2 centers). Efficacy

Wigley 1992 *(Continued)*

Participants	N=35 pts with Raynaud's phenomenon secondary to systemic sclerosis(7 men, 28 women, age 24-72years). 2 study sites involved:1 site involved treating pts as outpatients, pts treated as inpatients at site#2 Country: USA
Interventions	Diary: 2 weeks ac study 2 week outpatient washout period Iloprost (0.5-2.0ng/kg/min) or placebo over 6 hours IV for 5 consecutive days. Dose of iloprost increased in increments until pt developed side effects or a maximum dose of 2.0 ng/kg/min was reached
Outcomes	After week of IV infusions, pts followed as outpts and re-examined at 2, 4, 6, 8 and 10 weeks . Daily diaries completed by pt throughout duration of trial--# of attacks/day, duration of q attack and severity of attacks using a 4-point scale. Pts gaded overall Raynaud's symptoms ie. pain, numbness, burning, throbbing, impaired hand function with each episode of Raynaud's attack. Digital cutaneous lesions (digital ischemic ulcerations, fissures, and paronychia) counted, described and photographed at entry and on every followup assessment. Nailfold capillaroscopy performed by method of Maricq with photography at entry, at day 5 of infusion, and at week 2 and 10 of followup. Labs: plasma beta-thromboglobulin and platelet factor 4 made before infusion, during day 5 of infusion, and at 2, 6, and 10 weeks of followup. Pt global assessments at day 5 of infusion and biweekly throughout followup period. Measuring hemodynamic responses: strain gauge plethysmography and laser Doppler capillary velocimetry used at 1 site at entry, day 5 of infusion and at 2, 4, 6, 8, 10 weeks of followup. Site#2- strain gauge plethysmography only at entry, day 5 of infusion and at 2, 4, 6, 8, and 10 wwks followup. Duration of study: 10 weeks total
Notes	Quality Score=3

Wigley 1994

Methods	A randomized placebo-controlled clinical trial Multicentre Double blind . Efficacy Parallel design
Participants	131 pts with Raynaud's Phenomenon secondary to Systemic Sclerosis (101 women, 30 men) ages 20 to 79 years --all pts were outpatients at 12 centers. Criteria for pt entry: a minimum of 8 RP attacks per week documented by pt diary during 2 weeks ac first study day of infusion or 1 or more cutaneous ischemic finger lesions (ulcers, fissures, or paronychiae). Country: U.S.A.
Interventions	Pts randomly assigned to receive 1 of 2 parallel txs of 5 daily sequeuntial, 6-hour IV infusions of Iloprost 0.5 to 2.0 ng/kg per min or to receive a similar volume of Placebo Duration: 11 weeks
Outcomes	Frequency of RP attacks daily using a pt diary. Severity of RP attack using a 10-point, pt-completed scale Physician global assessment of RP severity recorded at 7 days ac infusion, on day 1 of infusion, during weeks 6 and 9 of follow-up period. Physician's overall rating of tx effect using a physician global assessment at baseline, 6 and 9 weeks.

Wigley 1994 *(Continued)*

	Digital cutaneous lesions recorded on days 1 and 5 of infusion and at weeks 3, 6, and 9 of follow-up period.
Notes	Quality Score = 4

Yardumian 1988

Methods	A randomized placebo-controlled clinical trial Double blind Efficacy Cross-over design with washout.
Participants	Twelve patients with severe secondary Raynaud's phenomenon Source of Population: Clinic Country: UK Mean age: 59
Interventions	3 day infusion of Iloprost or placebo Day 1-1 mg/kg/min Day 2-2 mg/kg/min Day 3-3 mg/kg/min followed by a six week washout period and then second treatment period
Outcomes	Diary cards: frequency, duration, severity of attacks Finger temperature and laser doppler flowmetry: prior, and at 1 and 6 weeks after infusons Platelet aggregation studies: start of first infusion and third infusion
Notes	Quality: 3

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

Study	Reason for exclusion
Belch 1983	Data not presented per subgroup; unable to include statistical data.
Lau 1991	Data not presented per subgroup; unable to include statistical data. Author to be contacted for further data.
McCune 1983	Not a randomized controlled trial
Mohrland 1985	Data presented combined with all subgroups. Unable to divide for eligible outcomes.
Torley 1991	Data not presented per subgroup; unable to include statistical data.
van den Hoogen 1994	Not a randomized controlled trial
Vayssairat 1996	Primary Raynaud's Phenomenon(not associated with scleroderma)
Wise 1994	Data not presented per subgroup; unable to include statistical data.

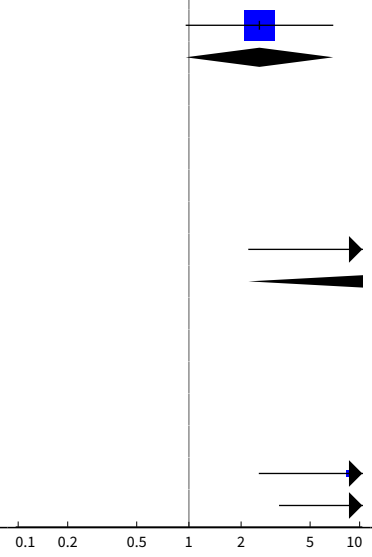
DATA AND ANALYSES

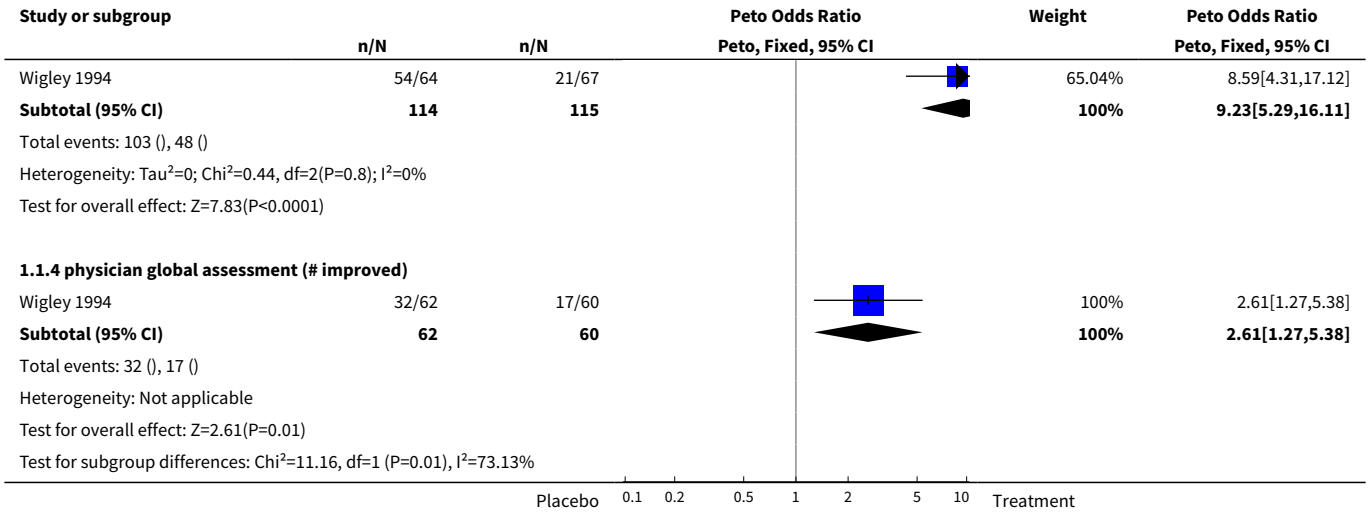
Comparison 1. Prostacyclin analogues

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Iloprost vs. Placebo	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 patient global assessment of improvement (# improved)	1	63	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.55 [0.96, 6.80]
1.2 number of digital ulcers healed	1	11	Peto Odds Ratio (Peto, Fixed, 95% CI)	23.17 [2.20, 243.52]
1.3 side effects	3	229	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.23 [5.29, 16.11]
1.4 physician global assessment (# improved)	1	122	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.61 [1.27, 5.38]
2 Cisaprost 2.5 ug vs. Placebo	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 global assessment of improvement (# improved)	1	32	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.33, 5.00]
2.2 side effects	1	32	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.76 [0.40, 7.65]

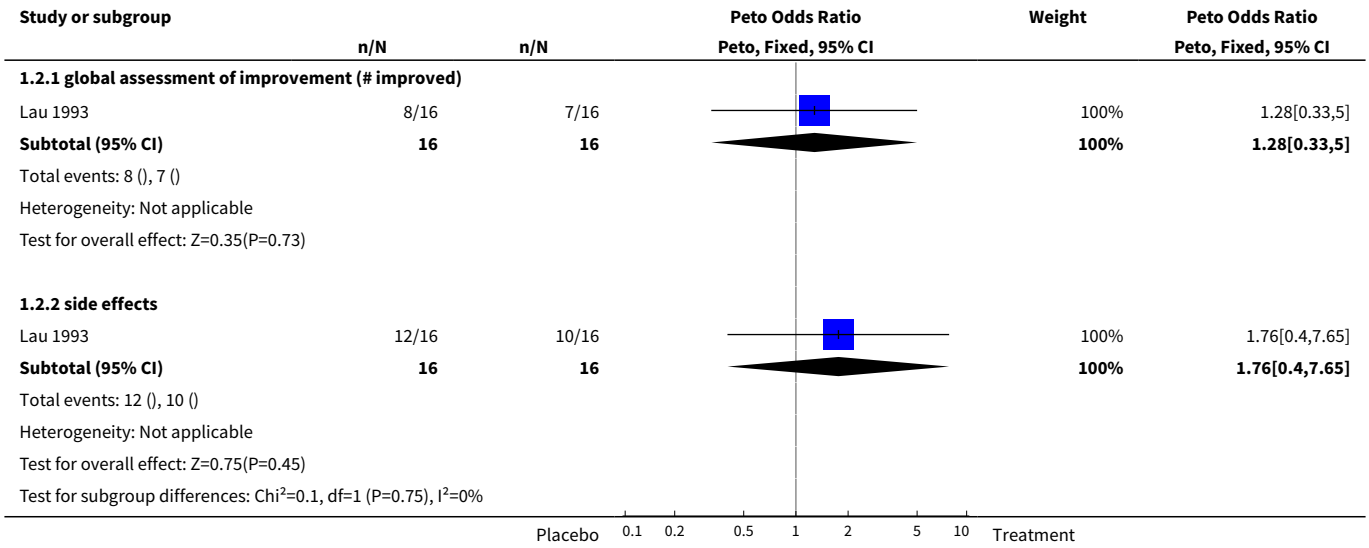
Analysis 1.1. Comparison 1 Prostacyclin analogues, Outcome 1 Iloprost vs. Placebo.

Study or subgroup	n/N	n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 patient global assessment of improvement (# improved)					
Belch 1995	20/32	12/31		100%	2.55[0.96,6.8]
Subtotal (95% CI)	**32**	**31**		**100%**	**2.55[0.96,6.8]**
Total events: 20 (), 12 ()					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.87(P=0.06)					
1.1.2 number of digital ulcers healed					
Wigley 1992	6/7	0/4		100%	23.17[2.2,243.52]
Subtotal (95% CI)	**7**	**4**		**100%**	**23.17[2.2,243.52]**
Total events: 6 (), 0 ()					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.62(P=0.01)					
1.1.3 side effects					
Belch 1995	31/32	19/31		21.11%	8.49[2.53,28.48]
Wigley 1992	18/18	8/17		13.85%	14.77[3.31,65.83]





Analysis 1.2. Comparison 1 Prostacyclin analogues, Outcome 2 Cisaprost 2.5 ug vs. Placebo.

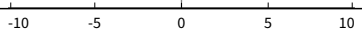


Comparison 2. Iloprost vs. Placebo (Change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sign and Symptom Likert Score	1	35	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.38, 0.38]
2 Average Duration of Attacks	1	33	Mean Difference (IV, Fixed, 95% CI)	0.0 [-7.28, 7.28]
3 Severity Score	4	238	Mean Difference (IV, Fixed, 95% CI)	-0.69 [-1.12, -0.26]
4 frequency of attacks	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

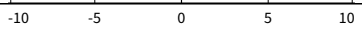
Analysis 2.1. Comparison 2 Iloprost vs. Placebo (Change from baseline), Outcome 1 Sign and Symptom Likert Score.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wigley 1992	18	1.3 (0.7)	17	1.3 (0.4)		100%	0[-0.38,0.38]
Total ***	**18**		**17**			**100%**	**0[-0.38,0.38]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Analysis 2.2. Comparison 2 Iloprost vs. Placebo (Change from baseline), Outcome 2 Average Duration of Attacks.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wigley 1992	17	9 (14)	16	9 (6)		100%	0[-7.28,7.28]
Total ***	**17**		**16**			**100%**	**0[-7.28,7.28]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

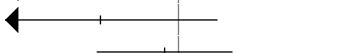


Analysis 2.3. Comparison 2 Iloprost vs. Placebo (Change from baseline), Outcome 3 Severity Score.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Belch 1995	32	0 (25.5)	31	-9 (25.5)		0.12%	9[-3.58,21.58]
McHugh 1988	11	-13.5 (2.5)	9	-4 (1)		7.08%	-9.5[-11.12,-7.88]
Wigley 1992	17	0.8 (1)	16	0.6 (0.5)		68.38%	0.21[-0.31,0.73]
Wigley 1994	62	2.7 (2.3)	60	3.4 (2.6)		24.43%	-0.69[-1.56,0.18]
Total ***	**122**		**116**			**100%**	**-0.69[-1.12,-0.26]**
Heterogeneity: Tau^2=0; Chi^2=128.05, df=3(P<0.0001); I^2=97.66%							
Test for overall effect: Z=3.13(P=0)							

Analysis 2.4. Comparison 2 Iloprost vs. Placebo (Change from baseline), Outcome 4 frequency of attacks.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Belch 1995	32	-27 (76.4)	31	7 (90.5)		0%	-34[-75.42,7.42]
McHugh 1988	11	-36 (2)	9	-13 (2.5)		0%	-23[-25.02,-20.98]
Wigley 1994	62	16.1 (16.2)	60	20.6 (21.4)		0%	-4.5[-11.25,2.25]
Yardumian 1988	6	3.7 (3.2)	6	4.5 (3.7)		0%	-0.8[-4.71,3.11]

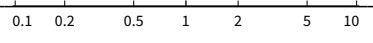


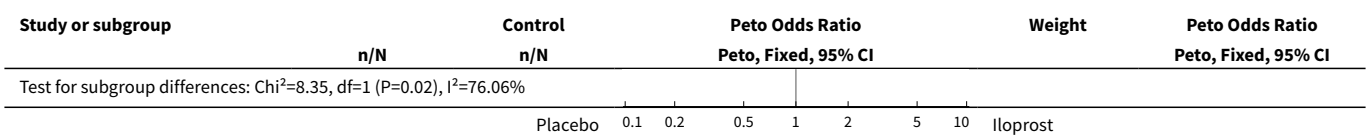
Comparison 3. Prostacyclin analogues

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Iloprost vs. Placebo (IV infusions only)	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 patient global assessment of improvement (# improved)	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 number of digital ulcers healed	1	11	Peto Odds Ratio (Peto, Fixed, 95% CI)	23.17 [2.20, 243.52]
1.3 side effects	2	166	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.44 [5.05, 17.67]
1.4 physician global assessment (# improved)	1	122	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.61 [1.27, 5.38]

Analysis 3.1. Comparison 3 Prostacyclin analogues, Outcome 1 Iloprost vs. Placebo (IV infusions only).

Study or subgroup	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.1.1 patient global assessment of improvement (# improved)				
Subtotal (95% CI)	**0**	**0**		**Not estimable**
Total events: 0 (), 0 (Control)				
Heterogeneity: Not applicable				
Test for overall effect: Not applicable				
3.1.2 number of digital ulcers healed				
Wigley 1992	6/7	0/4	100%	23.17[2.2,243.52]
Subtotal (95% CI)	**7**	**4**	**100%**	**23.17[2.2,243.52]**
Total events: 6 (), 0 (Control)				
Heterogeneity: Not applicable				
Test for overall effect: Z=2.62(P=0.01)				
3.1.3 side effects				
Wigley 1992	18/18	8/17	17.56%	14.77[3.31,65.83]
Wigley 1994	54/64	21/67	82.44%	8.59[4.31,17.12]
Subtotal (95% CI)	**82**	**84**	**100%**	**9.44[5.05,17.67]**
Total events: 72 (), 29 (Control)				
Heterogeneity: Tau^2=0; Chi^2=0.42, df=1(P=0.52); I^2=0%				
Test for overall effect: Z=7.03(P<0.0001)				
3.1.4 physician global assessment (# improved)				
Wigley 1994	32/62	17/60	100%	2.61[1.27,5.38]
Subtotal (95% CI)	**62**	**60**	**100%**	**2.61[1.27,5.38]**
Total events: 32 (), 17 (Control)				
Heterogeneity: Not applicable				
Test for overall effect: Z=2.61(P=0.01)				

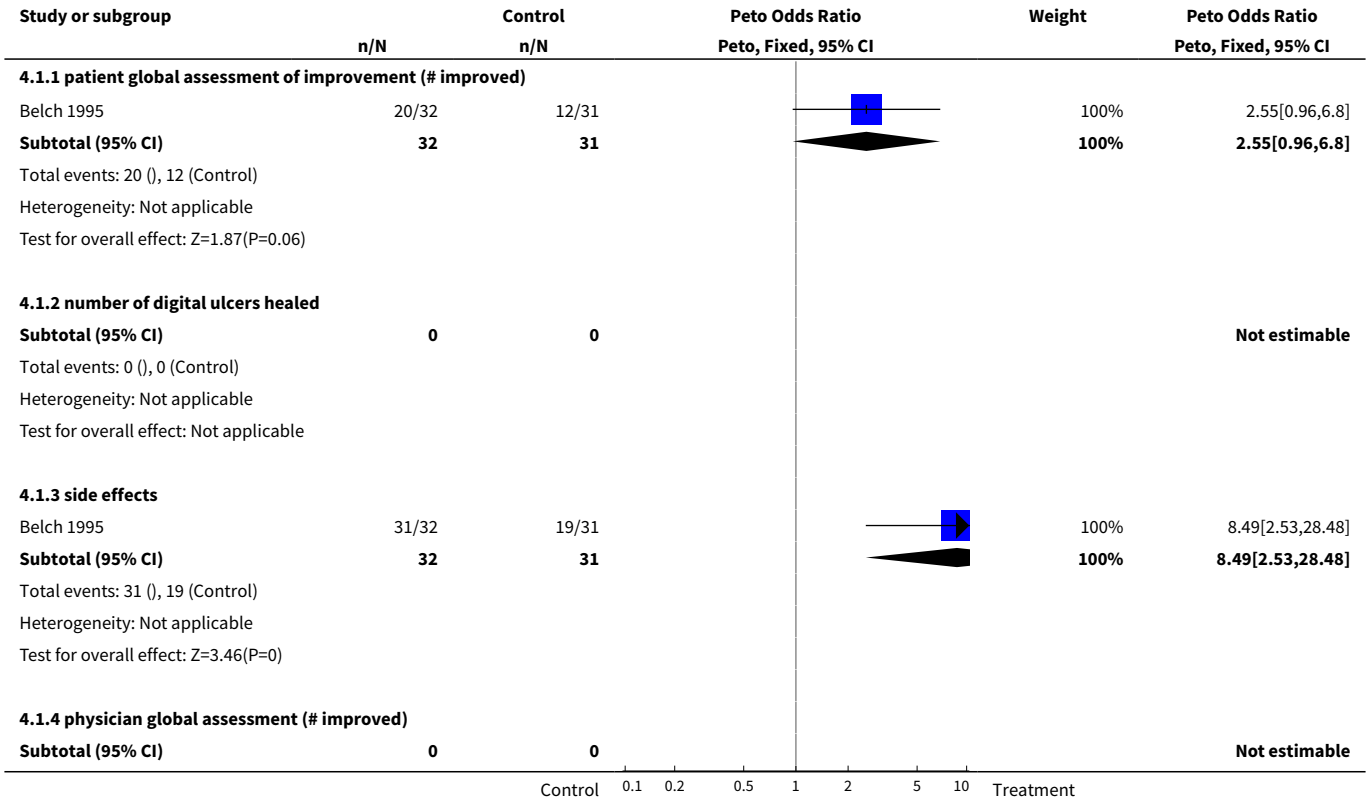


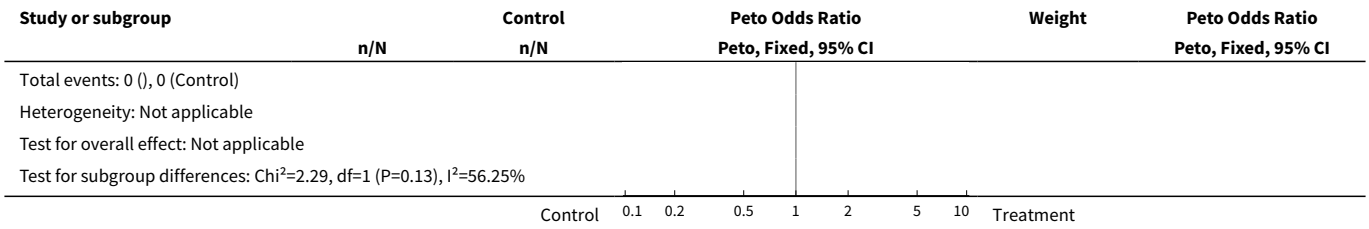


Comparison 4. Prostacyclin analogues

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral Iloprost vs. Placebo	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 patient global assessment of improvement (# improved)	1	63	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.55 [0.96, 6.80]
1.2 number of digital ulcers healed	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 side effects	1	63	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.49 [2.53, 28.48]
1.4 physician global assessment (# improved)	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Prostacyclin analogues, Outcome 1 Oral Iloprost vs. Placebo.





WHAT'S NEW

Date	Event	Description
29 August 2008	Amended	Converted to new review format. CMSG ID: C043-R

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- University of Western Ontario, London Ontario, Canada.
- Clinical Epidemiology Unit, Ottawa Hospital, Ontario, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Iloprost [*therapeutic use]; Raynaud Disease [*drug therapy] [*etiology]; Scleroderma, Systemic [*complications]; Vasodilator Agents [*therapeutic use]

MeSH check words

Humans