Management of intermittent claudication with pentoxifylline: meta-analysis of randomized controlled trials

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Abstract • Résumé

Objective: To evaluate the efficacy of pentoxifylline therapy in improving the walking capacity of patients with moderate intermittent claudication.

Data sources: A search of MEDLINE for trials published between 1976 and 1994 inclusive, and a bibliographic review of all articles retrieved.

Study selection: Randomized, placebo-controlled, double-blind clinical trials were selected that evaluated the pain-free walking distance (the distanced walked on a treadmill before the onset of calf pain) and the absolute claudication distance (the maximum distance walked on a treadmill) among patients with moderate intermittent claudication. Twelve study groups in 11 trials were included in the analysis.

Data extraction: In addition to information regarding the trial design, patient characteristics, dosages and treatment periods, the means and standard deviations were collected for both the pain-free walking and absolute claudication distances. Trial quality was also assessed.

Data synthesis: Overall, there was a statistically significant improvement in the pain-free walking distance after pentoxifylline therapy (weighted mean difference 29.4 m [95% confidence interval (CI) 13.0 to 45.9 m]); this finding was based on a total sample of 612 patients (308 in the treatment groups and 304 in the control groups). A significant improvement was also noted in the absolute claudication distance (weighted mean difference 48.4 m [95% CI 18.3 to 78.6 m]); this was based on a total sample of 511 patients (258 in the treatment group and 253 in the control group). In a sensitivity analysis of the pain-free walking distance, significant treatment effects and no statistically significant heterogeneity were found when only trials were included that were "medically eligible" (involved patients with stage II disease and a pain-free walking distance of 50 to 200 m). In a similar sensitivity analysis of the absolute claudication distance, the two conditions resulting in a significant treatment effect and no significiant heterogeneity were the inclusion of "medically eligible" trials and those with a shorter treatment duration (13 weeks or less).

Conclusion: Pentoxifylline therapy may be efficacious in improving the walking capacity of patients with moderate intermittent claudication. However, properly conducted clinical trials are required to provide a true estimate of the benefit.

Objectif : Évaluer l'efficacité de la thérapie à la pentoxifylline pour améliorer la capacité de marche des patients souffrant de claudication intermittente modérée.

Sources de données : Recherche dans MEDLINE d'études publiées entre 1976 et 1994 inclusivement et revue bibliographique de tous les articles extraits.

Sélection d'études : On a choisi des études cliniques randomisées à double insu contrôlées par placebo au cours desquelles on a évalué la distance de marche sans douleur (distance parcourue sur un tapis roulant avant l'apparition de la douleur au mollet) et la distance absolue de claudication (distance maximale parcourue sur un tapis roulant) chez les patients atteints de claudication inter-

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mittente modérée. L'analyse a porté sur 12 groupes d'étude et 11 études.

Extraction de données : Outre l'information sur la conception de l'étude, les caractéristiques des patients, les posologies et les périodes de traitement, on a calculé les moyennes et les écarts types dans le cas à la fois de la distance de marche sans douleur et de la distance absolue de claudication. On a évalué aussi la qualité de l'étude.

Synthèse des données : Dans l'ensemble, on a constaté une amélioration significative sur le plan statistique de la distance de marche sans douleur après une thérapie à la pentoxifylline (différence moyenne pondérée de 29,4 m [intervalle de confiance (IC) à 95 %, 13,0 à 45,9 m]). Cette constatation était fondée sur un échantillon total de 612 patients (308 dans les groupes de traitement et 304 dans les groupes témoins). On a constaté aussi une amélioration significative de la distance absolue de claudication (différence moyenne pondérée de 48,4 m [IC à 95 %, 18,3 à 78,6 m]). Cette constatation était fondée sur un échantillon total de 511 patients (258 dans le groupe de traitement et 253 dans le groupe témoin). Dans le cadre d'une analyse de sensibilité de la distance de marche sans douleur, on a constaté des effets significatifs du traitement et aucune hétérogénéité significative sur le plan statistique lorsqu'on n'a inclus que des études «admissibles sur le plan médical» (patients atteints de la maladie au stade II et distance de marche sans douleur de 50 à 200 m). Dans le cadre d'une analyse semblable de sensibilité portant sur la distance absolue de claudication, les deux conditions qui ont produit un effet significatif du traitement et aucune hétérogénéité significative ont été l'inclusion des études «admissibles sur le plan médical» et de celles où la durée du traitement était plus courte (13 semaines ou moins).

Conclusion : La thérapie à la pentoxifylline peut être efficace et améliorer la capacité de marche des patients atteints de claudication intermittente modérée. Il faut toutefois effectuer des études cliniques en bonne et due forme si l'on veut établir une véritable estimation de l'avantage.

Intermittent claudication is a symptom of peripheral vascular disease and presents as debilitating pain in the leg muscles that greatly reduces the mobility of patients. Improvement in walking capacity should be considered as a therapeutic aim, because intermittent claudication represents the essential clinical symptom of the patient. The two measures of walking capacity most commonly used to assess the severity of claudication are the pain-free walking distance (the distance walked on a treadmill before the onset of pain) and the absolute claudication distance (the maximum distance walked on a treadmill).[1]

Currently the only drug approved by the US Food and Drug Administration to treat intermittent claudication is pentoxifylline. It is thought to decrease blood viscosity and platelet activity, thereby increasing red blood cell flexibility.[2] The result is increased blood flow through the capillaries and improved tissue oxygenation. Although many similar clinical trials have been performed since the 1970s, it is still unclear whether pentoxifylline is clinically efficacious in improving the walking capacity of patients.

Several reviews evaluating the efficacy of pentoxifylline have been published.[3–6] Rossner and Muller[3] and Ernst[6] concluded that pentoxifylline was effective in improving patients' walking distance, yet Cameron and associates[4] and Radack and Wyderski[5] concluded that the limited amount and quality of reported data from the trials analysed precluded an overall, reliable estimate of the drug's efficacy. However, none of the four reviews satisfied the criteria for systematically pooling individual trials.[7,8]

We therefore conducted a meta-analysis primarily to determine whether pentoxifylline is effective in improving the walking capacity of patients with moderate intermittent claudication. The measures of interest were the pain-free walking distance and the absolute claudication distance.

Methods

Literature search and study selection

Two main search strategies were used: a search of MEDLINE for articles published between 1976 (the year in which the first controlled trial using pentoxifylline was published) and 1994 inclusive, and a review of the references cited in the retrieved articles. The MeSH terms used in the database search were "peripheral vascular disease," "pentoxifylline" and "intermittent claudication." No restrictions for the language of publication or the study design were made.

We attempted to contact all corresponding authors of the published trials for which there were incomplete data. We also consulted several content experts for information about the existence of any unpublished or current pentoxifylline trials.

For inclusion in our analysis trials had to meet the following criteria: randomized, placebo-controlled, double-blind clinical trial; patients had moderate intermittent claudication due to peripheral vascular disease at stage II or III according to Fontaine's classification (pain-free walking distance of 50 to 200 m, or less than 50 m, respectively[9–11]); the duration of the intermittent claudication ranged from more than 3 months to less than 5 years; the intervention was therapy with pentoxifylline, 600 to 1800 mg/d, lasting from 2 to 26 weeks;

and the outcomes of measure were pain-free walking distance and absolute claudication distance. Single-blind and open studies were not considered because of evidence of a large placebo response in claudication trials.[4,12,13] Crossover trials were considered for inclusion, but only data from the first phase of the trials were used in the analysis, in order to avoid misinterpretation of the results.

Assessment of trial quality

We assessed the quality of reporting of each trial using a validated three-item scale.[14] The items assessed the quality of randomization, double-blinding, and inclusion of data for dropouts and withdrawals. The scale ranges in scores from 0 to 5, higher scores indicating a superior quality of reporting. The trials were scored under masked conditions (the authors, their affiliations, all journal identifiers, references and funding sources were deleted using a black marker), and final scores were obtained through group consensus.

Data collection

We collected information regarding the trial design, patient characteristics, dosages and treatment periods. We attempted to collect data from each trial on the means and standard deviations (SDs) for the pain-free walking and absolute claudication distances; however, this proved difficult, because there were numerous data-reporting inconsistencies.

The standard method of reporting the results was to give the number of metres walked on the treadmill. In one trial[15] the results were given in seconds walked on the treadmill, so we calculated the number of metres using the reported speed of the treadmill (4 km/h). In another trial[16] the number of paces rather than metres was given for the pain-free walking distance, so we estimated the equivalent number of metres using a conversion factor of 6, given the age and disease severity of the patients.

Statistical analysis

Data on the pain-free walking distances (from 10 trials[2,9,10,15–21]) and on the absolute claudication distances (from 7 trials[2,9,10,16,17,19,22]) were pooled to arrive at an overall estimate of the effectiveness of pentoxifylline. These data were presented both as a weighted mean difference and an effect size.[23] Also, we evaluated between-trial heterogeneity using Cochran's Q-test[23] and performed a sensitivity analysis of trial quality, dosages, treatment duration and disease severity. With respect to disease

Table I: Randomized controlled trials of pentoxifylline therapy for intermittent claudication (IC)*

Study	No. of male (and female) patients	No. of patients completing study	Fontaine stage of disease	Duration of IC	Pentoxifylline dosage,† mg/d	Duration of treatment, wk
Rudofsky et al, 1989[1] (Germany)	133 (26)	154	II	> 6 mo	600 IV	2
Lindegarde et al, 1989[9] (Sweden and Denmark)	119 (31)	150	II	> 6 mo	1200	26
Ernst et al, 1992[10] (Austria)	34 (6)	40	II	> 3 mo	1200	12
Porter et al, 1982[11] (United States)	105 (23)	82	II	> 6 mo	§	24
Thomson et al, 1990[15] (United Kingdom)	4 (11)	13	II–III	NR‖	¶	12
Reilly et al, 1987[16] (England)	30	25	II	> 6 mo	NR	8
Donaldson et al, 1984[18] (England)	62 (18)	73	II	NR	600	8
Roekaerts et al, 1984[19] (Belgium)‡	3 (17)	20	II–III	2–5 yr	1200	12
Roekaerts et al, 1984[19] (Belgium)	3 (13)	16	II–III	3–5 yr	1200	24
Strano et al, 1984[20] (Italy)‡	12 (6)	18	II–III	> 4 mo	800	12
Bollinger et al, 1977[21] (Switzerland)	17 (2)	19	II	1.5 yr	600	8
Di Perri et al, 1983[22] (Italy)‡	19 (5)	24	II	1–5 yr	1200	8

*All trials were double-blind, placebo-controlled.
†Unless otherwise specified, medication was administered in tablet form. IV = intravenously.
‡Crossover trial (only the first phase was considered for analysis).
§Dose was increased stepwise from 600 to 1200 mg/d.
‖NR = not reported.
¶ Dosage was 600 mg/d intravenously plus 400 mg orally three times daily for the first 5 days, then 400 mg orally three times daily.

severity, trials were defined as "medically eligible" if the patients had Fontaine's stage II disease.

Results

We found 20 trials of pentoxifylline efficacy through the MEDLINE search and an additional 9 through the bibliographic search. Group consensus determined that 12 trials did not meet the eligibility criteria: 1 involved patients with Fontaine's stage IV disease,[24] 8 were not conducted in a randomized fashion,[25–32] 2 were not placebo-controlled trials[33,34] and 1 was not performed in a double-blind fashion.[35] In addition, two German articles could not be obtained.[36,37] Four trials[11,38–40] had to be excluded because the data could not be converted into the required descriptive statistics and follow-up with the trial investigators did not resolve these issues. Thus, a total of 12 study groups from 11 trials were included in the meta-analysis (Table 1).

The baseline pain-free walking distances of the patients are given in Table 2. The pooled data on the effect of pentoxifylline on the pain-free walking and absolute claudication distances, as well as the quality scores assigned to the 12 study groups, are given in Table 3.

Table 2: Baseline pain-free walking distances (in metres)

	Treatment group			Placebo group		
Trial	Minimum distance	Maximum distance	Mean (and SD)	Minimum distance	Maximum distance	Mean (and SD)
Rudofsky[1]	112	126	119 (7)	110	126	116 (6)
Lindegarde[9]	73	81	77 (4)	75	81	79 (4)
Ernst[10]	132	156	144 (12)	120	156	134 (14)
Porter[11]	98	124	111 (13)	105	124	172 (16)
Thomson[15]	36	56	46 (10)	40	56	53 (13)
Reilly[16]	76	102	89 (13)	69	102	93 (24)
Donaldson[18]	93	123	108 (15)	86	123	97 (11)
Roekaerts[19]	351	569	460 (109)	300	569	432 (132)
Roekaerts[19]	168	238	203 (35)	151	238	188 (37)
Strano[20]	116	126	121 (5)	128	126	134 (6)
Bollinger[21]	192	260	226 (34)	148	260	177 (29)

*The trial by Di Perri et al[22] did not meet the stage II requirements for baseline walking distances (determined from the text of the article).

Table 3: Quality scores of trials and distances achieved after pentoxifylline therapy

		Pain-free distance,‡ m				Absolute claudication distance,§ m			
		Treatment group		Placebo group		Treatment group		Placebo group	
Trial	Quality score*	Mean (and SD†)	No. of patients	Mean (and SD)	No. of patients	Mean (and SD)	No. of patients	Mean (and SD)	No. of patients
Rudofsky[1]	2	217 (142)	75	162 (79)	79	360 (250)	75	287 (215)	79
Lindegarde[9]	3	139 (145)	76	126 (120)	74	198 (155)	76	200 (138)	74
Ernst[10]	2	364 (236)	20	384 (228)	20	504 (257)	20	420 (229)	20
Porter[11]	4	195 (171)	42	180 (152)	40	268 (199)	42	250 (172)	40
Thomson[15]	3	141 (104)	9	61 (34)	6	–		–	
Reilly[16]	3	116 (69)	15	170 (118)	10	175 (137)	15	191 (158)	10
Donaldson[18]	3	119 (74)	34	129 (109)	39	–		–	
Roekaerts[19]	3	1029 (696)	10	555 (515)	10	1228 (753)	10	742 (629)	10
Roekaerts[19]	4	458 (212)	8	130 (51)	8	555 (252)	8	190 (85)	8
Strano[20]	3	175 (38)	9	139 (22)	9	–		–	
Bollinger[21]	3	697 (396)	10	270 (605)	9	–		–	
Di Perri[22]	4	–		–		360 (99)	12	215 (98)	12

*Quality was defined as "providing information about the completeness of reporting of randomization, double-blinding, and dropouts and withdrawals to avoid biases in intervention comparisons"; a trial received 2 points if it was described as randomized and the appropriate method was reported, another 2 points if it was described as double-blind and the appropriate method was reported, and another point if the number of withdrawals and dropouts were reported, and the reasons given, by intervention group (see the study by Jadad et al[14] for additional information regarding the scales).
†SD = standard deviation.
‡Distance walked on a treadmill before the onset of pain.
§Maximum distance walked on a treadmill.

The results of the sensitivity analysis on the effect of pentoxifylline on the pain-free walking distance, based on data from 11 study groups in 10 trials, are shown in Table 4. The total sample size was 612 patients (308 in the treatment group and 304 in the placebo group). The overall weighted mean difference of 29.4 metres was statistically significant (95% CI 13.0 to 45.9 m), which indicated that subjects in the treatment group walked on average about 30 m further than those not taking the drug.

The overall weighted mean difference of 48.4 m for the absolute claudication distance (Table 5) was also statistically significant (95% CI 18.3 to 78.6 m). This sensitivity analysis was based on the results from six trials and seven study groups, for an overall sample size of 511 patients (258 in the treatment group and 253 in the control group).

Between-trial heterogeneity was statistically significant when all of the trials were included in the analysis. This heterogeneity was explored using sensitivity analysis. The four main sources of this variation that were analysed included the overall quality of the trials (the scores ranged from 2 to 4 [Table 3]), the drug dosages, the duration of treatment and, most important, the severity of disease (as determined by the large differences from baseline pain-free walking distances [Table 2]).

In the sensitivity analysis of pain-free walking distance, significant treatment effects and no statistically significant heterogeneity were found when only "medically eligible" trials were included.[2,9,10,16–18,20] In comparison, for the absolute claudication distance, the two conditions that resulted in a significant improvement and no statistically significant heterogeneity were the inclusion of "medically eligible" trials[9,16,17] and those with a shorter treatment duration (13 weeks or less).[2,16,19,20,22]

Table 4: Sensitivity analysis of trials for effect of pentoxifylline therapy on pain-free walking distance

Trials	Overall improvement in distance (and 95% CI*), m	Overall effect size	χ^2 value†	Homogeneity
All trials	29.4 (13.0 to 45.9)	0.3	9.2	25.6
High-quality trials‡	23.4 (4.7 to 42.1)	0.2	3.9	22.8
Medically eligible trials§	22.8 (5.9 to 39.7)	0.2	3.5	12.5¶
High-quality, medically eligible trials	14.3 (–5.0 to 33.6)	0.1	0.2	7.1¶
Trials using a standard dosage‖	36.5 (4.6 to 68.4)	0.2	3.4	13.1
Trials with treatment duration of ≤ 13 wk	29.0 (10.4 to 47.6)	0.3	7.8	15.8
Trials with treatment duration of > 13 wk	30.8 (–4.6 to 66.3)	0.2	1.9	9.3

*CI = confidence interval.
†1 degree of freedom.
‡Trials with a quality score of 3 or more.
§Trials that included only patients who had Fontaine's stage II disease and a pain-free walking distance of 50 to 200 m.
‖Defined as 1200 mg/d of pentoxifylline, in accordance with the Canadian Pharmaceutical Association guidelines.[2]
¶Statistically significant.

Table 5: Sensitivity analysis of trials for effect of pentoxifylline therapy on the absolute claudication distance

Trials	Overall improvement in distance (and 95% CI), m	Overall effect size	χ^2 value*	Homogeneity
All trials	48.4 (18.3 to 78.6)	0.3	8.0	19.0
High-quality trials	41.3 (7.4 to 75.1)	0.2	3.3	18.2
Medically eligible trials	19.7 (–13.5 to 52.8)	0.1	2.3	2.8†
High-quality, medically eligible trials	1.0 (–37.4 to 39.4)	0.0	0.0	0.3†
Trials using standard dosage	48.6 (14.1 to 83.0)	0.3	5.0	17.7
Trials with treatment duration of ≤ 13 wk	87.2 (40.9 to 133.5)	0.4	9.5	7.2
Trials with treatment duration of > 13 wk	19.8 (–19.8 to 59.5)	0.1	0.7	9.0

*1 degree of freedom.
†Statistically significant.

Discussion

The results of our meta-analysis show that pentoxifylline can be efficacious in improving the walking capacity of people with moderate claudication. However, depending on the perspective (e.g., the doctor's, the patient's or the policymaker's), an increase of 30 m in the pain-free walking distance may or may not be clinically significant. The ability to walk a distance of about 70 m (the length of an average city block) without pain enables patients to be fairly self-sufficient, to work in a non-physical job and to participate in most social activities.[41] In addition, distances walked on a treadmill can be approximated to those walked on flat ground by multiplying them by a factor of 3.[42] Thus, our results suggest that pentoxifylline therapy may also be clinically beneficial, since the equivalent distance walked on flat ground would be about 90 m.

These results only pertain to the efficacy of pentoxifylline and not necessarily to its effectiveness. No subgroup analysis could be performed, because even though some of the trials reported the numbers of patients who smoked, had diabetes or had hypertension in the treatment and control groups, the measurements of pain-free walking and absolute claudication distances were not presented separately for these subgroups. In addition, there were dropouts from a large number of trials; however, only data for those who completed the trial were published. Thus, most of the reported data were not for the intention-to-treat groups.

Many factors, other than the four mentioned in the sensitivity analysis (study quality, dosages, treatment duration and severity of disease), could affect the potential effectiveness of the drug and may have contributed to the finding of statistically significant heterogeneity when all trials were combined. For instance, the mean age of the patient groups studied varied from 51 to 70 years; the sociodemographic characteristics undoubtedly varied, given that the studies were conducted in different countries, including the United States, the United Kingdom and Scandinavia; the use of concomitant drugs by the trial participants was often mentioned, but few studies excluded patients based on this information; most of the patients were men, although in two trials[15,19] the number of women was greater; finally, and perhaps most important, the sample sizes of the trials ranged from 13 to 154. It has been suggested that a sample of 40 patients is required to detect a clinically important difference in walking capacity (greater than 40% between placebo and treatment groups), with the necessary statistical power, and an acceptable level of significance.[3] Only five trials[2,9,10,17,18] met this criterion.

Although we attempted to minimize bias, one limitation that persisted was the extraction of data from published trials. There seemed to be little consistency in the type of data reported, and in more than 25% of the eligible trials standard descriptive statistics were not presented and insufficient data were provided to calculate them. This problem is commonly noted by reviewers, and the fact that these difficulties continue emphasizes the need for some form of structured reporting of randomized clinical trials.[43] Also, there may have been a potential language bias, because we could not retrieve two German trials.

Costs are important when comparisons are made with other drugs or forms of therapy. Stegarchis and collaborators[44] reported that, on average, pentoxifylline accounted for almost 10% of the total cost of care among patients using the drug on a continuous basis, and local costs for the drug are about $1000 per year (Ottawa Civic Hospital pharmacy: unpublished data). Pentoxifylline is currently not covered by some provincial health plans. Another important issue when conducting trials of such a potentially debilitating disease is quality of life.

Conclusion

The results of our meta-analysis show that pentoxifylline therapy can be efficacious, in terms of both clinical and statistical significance, in improving both the pain-free walking distance and the absolute claudication distance among patients with moderate intermittent claudication. However, because there were numerous methodological differences among the trials analysed, a properly conducted large multicentred clinical trial is required to provide a true estimate of benefit. Such a trial should also examine issues of cost and quality of life.

Clinical relevance: Pentoxifylline appears to be effective in improving the walking capacity of patients with moderate intermittent claudication. Treated patients were able to walk, on average, 30 m farther than control patients on a treadmill (equivalent to 90 m on flat ground).

Study limitations: Whether pentoxifylline is more or less effective in patients who are elderly, smoke or have diabetes, hypertension or other conditions is unknown; the cost-effectiveness of this medication and its impact on quality of life have yet to be determined.

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