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[Intervention Review]

Pentoxifylline for diabetic retinopathy

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ABSTRACT

Background

There is increasing evidence that capillary occlusion plays an important part in the development of diabetic retinopathy. Disaggregants, such as pentoxyfilline may influence the outcome and progression of diabetic retinopathy, but no systematic review of the literature on its efficacy and safety has been published to examine this hypothesis.

Objectives

The aim of the current research was to review the literature in a systematic way in order to assess the effects of pentoxyfilline for diabetic retinopathy in methodologically robust trials. The null hypothesis was that pentoxyfilline has no influence on the progression of diabetic retinopathy or blindness.

Search methods

A systematic search of electronic databases was carried out to identify publications. Relevant papers, written in any language, were accessed and assessed for data.

Selection criteria

Only randomized controlled clinical trials (RCTs) evaluating the effects of pentoxyfilline in the treatment of diabetic retinopathy were to be included.

Data collection and analysis

Two authors independently assessed studies for inclusion criteria and for risk of bias.

Main results

A total of 97 publications were identified by the electronic search and two authors checked the abstracts. Of these, 17 were identified as potentially relevant trials providing information about treatment of patients with diabetic retinopathy using pentoxyfilline and were read in full. Unfortunately, no publication fulfilled our inclusion criteria.

Authors' conclusions

No sound research to date has examined the treatment of diabetic retinopathy with pentoxyfilline in such a way as to indicate whether this form of intervention has a significant impact on the natural history of this clinical condition. The potential role of this substance in the treatment of diabetic retinopathy remains open to debate, and it is suggested that future research focusing on patient-relevant outcomes takes the opportunity of addressing this important issue directly.

PLAIN LANGUAGE SUMMARY

Pentoxifylline for diabetic eye disease

Diabetic retinopathy or eye disease is the leading cause of blindness in developed countries. Nowadays its treatment is based on the use of laser therapy. Since this is a procedure which destroys important cells in the eye, drug approaches have been developed to prevent or improve lesions in the eyes of diabetic people. Studies with the agent pentoxyfilline suggest this may have an important role in the outcome and progression of diabetic retinopathy.
Unfortunately, a thorough search for high quality data did not reveal appropriate studies.

BACKGROUND

Description of the condition

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. A consequence of this is chronic hyperglycaemia (that is elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy. The risk of cardiovascular disease is increased. For a detailed overview of diabetes mellitus, please see under 'Additional information' in the information on the Metabolic and Endocrine Disorders Group in *The Cochrane Library* (see 'About', 'Cochrane Review Groups (CRGs)'). For an explanation of methodological terms, see the main glossary in *The Cochrane Library*.

During the first two decades of the disease, nearly all patients with type 1 diabetes and more than 60% of patients with type 2 diabetes develop retinopathy. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 3.6% type 1 and 1.6% type 2 diabetes patients were legally blind. In the younger-onset group, 86% of blindness was attributed to diabetic retinopathy. In the older-onset group, one-third of legal blindness was associated with diabetic retinopathy (Klein 1984).

Diabetic retinopathy is detected clinically by the presence of visible ophthalmoscopic retinal microvascular lesions in an individual with diabetes mellitus. Retinopathy can be classified as non-proliferative (NPDR) and proliferative diabetic retinopathy (PDR). NPDR is again divided into NPDR with maculopathy, NPDR without maculopathy and pre-proliferative retinopathy.
NPDR indicates progressive ischemia in the retina and an increased risk for the development of PDR and blindness. The prominent features of NPDR include microaneurysms, dot or blot haemorrhages, venous abnormalities, hard yellow exudates, intraretinal microvascular abnormalities, and cotton wool spots. Maculopathy is defined as the presence of oedema, haemorrhages, exudates, retinal thickening within five mm of the fovea, with or without visual loss or a combination of these factors. Pre-proliferative diabetic retinopathy is the stage before the onset of neovascularization and is characterized by extensive retinal haemorrhages, marked venous beading, numerous cotton wool spots or retinal infarcts, intra-retinal microvasculature abnormalities and marked retinal ischemia as evidenced by capillary drop-outs in the fundus fluorescein angiogram. Proliferative diabetic retinopathy is characterized by retinal new vessels, fibrous tissue, pre-retinal haemorrhage, vitreous haemorrhage, vitreoretinal traction and localized retinal detachment.
Laser photocoagulation is the primary means by which ophthalmologists control the progression of macular oedema and neovascularization. Since this is an invasive procedure destroying retinal cells, pharmacotherapeutic approaches were developed to prevent or regress retinal lesions in diabetic people (Balasubramanyam 2002).

Description of the intervention

Pentoxifylline (1-[5-oxohexyl]-3,7-dimethylxanthine) is a xanthine derivative. It is used in the treatment of intermittent claudication from chronic occlusive arterial disease. Clinical trials show that pentoxifylline may increase walking distance before the beginning of claudication. Besides, there is evidence of an increase of blood flow in ischemic limbs of such patients, which reduces paraesthesia, cramps and rest pain. However, some investigators relate that just 20% to 30% of these patients may experience significant improvement of long duration. Pentoxifylline may also be beneficial in the treatment of diabetes associated vascular diseases. Usually, it takes two to six weeks before the favourable effects are evident. It appears that pentoxifylline has no vasodilator effect and therapeutic doses are not associated with significant changes of cardiac frequency or peripheral vascular resistance. Clinical responses to long-term oral administration of pentoxifylline appear to result primarily from the improvement of erythrocyte flexibility and from reduced blood viscosity; a reduced fibrinogen concentration may contribute to the latter one. A reduction in platelets and granulocytes' function may also be involved. However, the exact mechanism of action of pentoxifylline is currently poorly understood (Rall 1991).
Capillary occlusion is an early event in the development of diabetic retinopathy and, as was recently shown, leukocytes are involved in this process. Pentoxifylline improves deformability and decreases polymorphonuclear leukocytes F-actin content in normal individuals. Sonkin and co-workers showed, in a study with diabetic cats, a significant improvement in cellular deformability, in F-actin content and in superoxide production rate with the utilisation of pentoxifylline (Sonkin 1992).
Iwafune and co-workers furthermore demonstrated that diabetic individuals treated with pentoxifylline presented an earlier absorption of retinal haemorrhage and a significant lower appearance of neovascularization (Iwafune 1980). In some cases, there was a significant improvement in arm-retina time and a remarkable reduction of avascularized areas. Such results suggest pentoxifylline might be effective in preventing retinal or intra-retinal neovascularization and in improving recovery from these disorders.
A study elaborated by Ferrari and co-workers showed pentoxifylline to induce the normalisation of blood rheologic patterns and a significant decrease of total urinary protein and albumin excretion rates (Ferrari 1987). Such data suggest that pentoxifylline may play an important role in both the treatment of diabetic haemorrheological changes and renal disorders as well as in the prevention of accompanying degenerative vascular complications (Solerte 1985).

Adverse effects of the intervention

Most commonly reported adverse effects of pentoxifylline therapy involve the gastrointestinal tract (for example vomiting, inappetence). There are also reports of dizziness and headache occurring in a small percentage of humans receiving the drug. Other adverse effects (for example effects on the cardiovascular or central nervous system) have been reported as occurring rarely (Rall 1991).

Why it is important to do this review

Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20 to 74 years. That represents nearly all patients with type 1 and more than 60% with type 2 diabetes (Klein 1984).
In spite of its relevance, systematic reviews about pentoxifylline for diabetic retinopathy have not been performed. Therefore, this review attempts to investigate novel ways of preventing or slowing the progression of diabetic retinopathy.

OBJECTIVES

To assess the effects of pentoxifylline in the treatment of diabetic retinopathy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled clinical trials (RCTs) evaluating the effect of pentoxifylline on diabetic retinopathy.

Types of participants

We included any adult patient aged 20 to 75 years with diabetic retinopathy detected clinically by the presence of visible ophthalmoscopic retinal microvascular lesions.

To be consistent with changes in classification and diagnostic criteria of diabetes mellitus through the years, the diagnosis should have been established using the standard criteria valid at the time of the beginning of the trial (for example ADA 1997; ADA 1999; WHO 1980; WHO 1985; WHO 1998). Ideally, diagnostic criteria should have been described. If necessary, authors' definition of diabetes mellitus would be used. The same applies to diagnostic criteria of diabetic retinopathy. Diagnostic criteria would be eventually subjected to a sensitivity analysis.

Types of interventions

We considered the following types of intervention:

- pentoxifylline + photocoagulation versus placebo;
- pentoxifylline + photocoagulation versus no treatment + photocoagulation.

Types of outcome measures

Primary outcomes

We planned to evaluate the efficacy of pentoxyfilline for diabetic retinopathy by considering the following:

- progression of diabetic retinopathy defined as (1) the development of any retinopathy where none previously existed, (2) the development or progression of macular oedema with clinical significance as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS), and (3) the development of proliferative retinopathy from non-proliferative diabetic retinopathy or the recurrence of active proliferative diabetic retinopathy (Borrillo 1999);
- incidence of blindness.

Secondary outcomes

- mortality (all-cause mortality; diabetes related mortality (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyper- or hypoglycaemia or sudden death));
- morbidity (all-cause morbidity as well as diabetes and cardiovascular related morbidity, for example angina pectoris, myocardial infarction, stroke, peripheral vascular disease, neuropathy, retinopathy, nephropathy, erectile dysfunction, amputation);
- adverse effects;
- health-related quality of life;
- costs.

Covariates and effect modifiers

- duration of diabetes mellitus;
- duration of diabetic retinopathy;
- glycaemic control;
- blood pressure control;
- use of ACE inhibitors;
- presence of other systemic diseases.

Timing of outcome assessment

Depending on data.

Search methods for identification of studies

Electronic searches

We used the following sources for the identification of trials:

- *The Cochrane Library* (latest issue);
- MEDLINE (until July 2007);
- EMBASE (until July 2007);
- CINAHL (until July 2007);
- Web of Science (until July 2007).

We also searched databases of ongoing trials: Current Controlled Trials (www.controlled-trials.com - with links to other databases of ongoing trials).

The described search strategy (see for a detailed search strategy under Appendix 1) was used for MEDLINE. For use with EMBASE, *The Cochrane Library* and the other databases this strategy was slightly adapted.

Studies published in any language would be included.

Searching other resources

We planned to identify additional studies by searching the reference lists of included trials and (systematic) reviews, meta-analyses and health technology assessment reports noticed.

We contacted experts in order to identify unpublished research and trials still underway.

Data collection and analysis

Selection of studies

To determine the studies to be assessed further, two authors (CCLJ and OV) independently scanned the abstract, titles or both sections of every record retrieved. All potentially relevant articles were investigated as full text. Interrater agreement for study selection was measured using the kappa statistic (Cohen 1960). Differences would be marked and if these studies were later on included, the influence of the primary choice would be subjected to a sensitivity analysis. Where differences in opinion existed, they would be resolved by a third party. If resolving disagreement is not possible, the article would be added to those 'awaiting assessment' and authors would be contacted for clarification. An adapted QUOROM (quality of reporting of meta-analyses) flow-chart of study selection would be attached (Moher 1999).

Data extraction and management

For studies that fulfilled inclusion criteria, two authors (CCLJ and OV) would independently abstract relevant population and intervention characteristics using standard data extraction templates with any disagreements to be resolved by discussion, or if required by a third party. Any relevant missing information on the trial would be sought from the original author(s) of the article, if required.

Assessment of risk of bias in included studies

Two authors (CCLJ, OV) would assess each trial independently for risk of bias. Possible disagreement would be resolved by consensus, or with consultation of a third party in case of disagreement. We would explore the influence of individual quality criteria in a sensitivity analysis (see under 'sensitivity analyses'). Interrater agreement for key quality indicators would be calculated using the kappa statistic (Cohen 1960). In cases of disagreement, the rest of the group would be consulted and a judgement would be made based on consensus.

Dealing with missing data

Relevant missing data would be obtained from authors, if feasible. Evaluation of important numerical data such as screened, eligible and randomised patients as well as intention-to-treat (ITT) and per-protocol (PP) population would be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals would be investigated. Issues of missing daft, ITT and PP would be critically appraised and compared to specification of primary outcome parameters and power calculation.

Dealing with duplicate publications

In the case of duplicate publications and companion papers of a primary study, we would try to maximise yield of information by simultaneous evaluation of all available data. In cases of doubt, the original publication (usually the oldest version) would obtain priority.

Assessment of heterogeneity

In the event of substantial clinical or methodological or statistical heterogeneity, study results would not be combined by means of meta-analysis. Heterogeneity would be identified by visual inspection of the forest plots, by using a standard χ^2-test and a significance level of $\alpha = 0.1$, in view of the low power of such tests. Heterogeneity would be specifically examined with I^2 (Higgins 2002), where I^2 values of 50% and more indicate a substantial level of heterogeneity (Higgins 2003). I^2 demonstrates the percentage of total variation across studies due to heterogeneity and would be used to judge the consistency of evidence.
When heterogeneity is found, we will attempt to determine potential reasons for it by examining individual study characteristics and those of subgroups of the main body of evidence.

Assessment of reporting biases

Funnel plots would be used in an exploratory data analysis to assess for the potential existence of small study bias. There are a number of explanations for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to study size, poor methodological design of small studies and publication bias (Sterne 2001). Therefore, we planned to carefully use this tool (Lau 2006).

Data synthesis

Data would be summarised statistically if they were available, sufficiently similar and of sufficient quality. Statistical analysis would be performed according to the statistical guidelines referenced in the newest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses would be mainly performed if one of the primary outcome parameters demonstrated statistically significant differences between intervention groups. In any other case subgroup analyses would be clearly marked as a hypothesis generating exercise.

The following subgroup analyses were planned:

- age of patients (19 to less than 65 years, 65 years and above);
- different pentoxifylline doses;
- absence or presence of co-morbidities.

Sensitivity analysis

We would perform sensitivity analyses in order to explore the influence of the following factors on effect size:

- repeating the analysis excluding unpublished studies;
- repeating the analysis taking account of study quality, as specified above;
- repeating the analysis excluding any very long or large studies to establish how much they dominate the results;
- repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

The robustness of the results would also be tested by repeating the analysis using different measures of effects size (relative risk, odds ratio etc.) and different statistical models (fixed and random effects models).

RESULTS

Description of studies

We found no RCT which examined the treatment of diabetic retinopathy with pentoxyfilline.

Risk of bias in included studies

Methodological quality was not evaluated because of the absence of studies about the treatment of diabetic retinopathy with pentoxyfilline.

Effects of interventions

No sound research to date has examined the treatment of diabetic retinopathy with pentoxyfilline in such a way as to indicate whether the use of this substance has a significant impact on the natural history of the disease or on the incidence of blindness.

DISCUSSION

Capillary occlusion is an early event in the pathogenesis of diabetic retinopathy. There is evidence that pentoxifylline induces the normalisation of blood rheologic patterns and a significant decrease of total urinary protein and albumin excretion rates. Diabetic individuals treated with pentoxifylline presented an earlier absorption of retinal haemorrhage and a significant lower appearance of neovascularization. In some cases, there was a significant improvement in arm-retina time and a remarkable reduction of avascularized areas. These preliminary results suggest that pentoxifylline may be efficacious in preventing retinal or intra-retinal neovascularization and in improving recovery from these disorders. Therefore, disaggregants like pentoxyfilline may provide additional beneficial effects for patients with diabetic retinopathy. However, no sound RCT investigated this hypothesis.

AUTHORS' CONCLUSIONS

Implications for practice

In the absence of sound studies with pentoxyfilline treatment of diabetic retinopathy, laser photocoagulation remains the primary treatment of such clinical condition.

Implications for research

Since laser photocoagulation is an invasive procedure which destroys retinal cells, novel approaches should be developed to prevent or regress retinal lesions in diabetic people. The role of capillary occlusion in the pathogenesis of diabetic retinopathy and the potential therapeutic effect of pentoxyfilline in the treatment of such clinical disorder remains open to debate, and it is suggested that future research focusing on patient-relevant outcomes takes the opportunity of addressing this important issue directly.

ACKNOWLEDGEMENTS

This review was developed in cooperation with the German Cochrane Centre and the Department of General Practice, Clinical Centre of the Heinrich-Heine University in Duesseldorf, Germany.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Bloomgarden 1999	Review article.
Desai 2007	Review article.
Gincherman 1982	The aim of this article was to study haemocoagulation in 78 patients with diabetes mellitus during the treatment of diabetic retinopathy with antiaggregating and haemostatic drugs.
Gol'tseva 1983	Groups from the article are different of those from the protocol.
Ivanisevic 1994	Review article.

Study	Reason for exclusion
Iwafune 1980	The aim of this study was to evaluate the effect of pentoxyfilline given orally to patients with retinal haemorrhage caused by disturbances of retinal circulation, i.e. branch and/or total obstruction of the central retinal vein, obstruction of the central retinal artery, diabetic retinopathy and polycythaemic retinopathy.
Katznelson 1980	The aim of this article was to evaluate the effect of pentoxyfilline on the oxygenation of the anterior chamber humour and the bioelectrical activity of the retina.
McCarty 1998	Review article.
Parikh 2004	Review article.
Polunin 1993	Article is different from the reference.
Radfar 2005	Groups from the article are different of those from the protocol.
Saldan 1984	The aim of this article was to reveal the role of coagulative shift of blood in pathogenesis of diabetic retinopathy.
Schubotz 1975	No RCT, no investigation of diabetic retinopathy.
Schubotz 1975a	No RCT, no investigation of diabetic retinopathy.
Solerte 1985	The aim of this article was to evaluate erythrocyte filtrability, reduction in fibrinogen levels, proteinuria and albumin excretion rate.
Sonkin 1993	The aim of this study was to determine if oral pentoxyfilline would improve retinal microvascular haemodynamics and blood rheology in patients with diabetes.
Wroe 2001	Conference report.

APPENDICES

Appendix 1. Search strategy

Search terms
Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) = to substitute for one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent.
MEDLINE:
I. Pentoxifylline:
1. exp Pentoxifylline/ 2. (pentoxifyllin$ or trental or torental or agapurin).ab,ti,ot. 3. bl-191.ab,ti,ot. 4. 6493-05-6.rn. 5. exp Phosphodiesterase inhibitors/ 6. phosphodiesterase inhibitor$.ab,ti,ot. 7. or/1-6

(Continued)

II. Diabetic retinopathy:

8. exp Diabetic Retinopathy/

III. Eye diseases:

9. exp Retinal Detachment/
10. exp Retinal Degeneration/
11. exp retinal hemorrhage/ or exp retinal neovascularization/ or exp vitreoretinopathy, proliferative/
12. vitreous detachment/ or vitreous hemorrhage/
13. (eye diseas$ or blindness or visual loss$ or vitrectom$ or cataract$).ab,ti,ot.
14. retina$ detachment$.ab,ti,ot.
15. vitreous haemorrhag$.ab,ti,ot.
16. vitreous hemorrhag$.ab,ti,ot.
17. (macular adj (oedema or edema)).ab,ti,ot.
18. microaneurysm$.ab,ti,ot.
19. neovascular$.ab,ti,ot.
20. fibrous tissue$.ab,ti,ot.
21. (retinopath$ or retinitis or maculopath$).ab,ti,ot.
22. (macula defect$ or macula degeneration$).ab,ti,ot.
23. (macula$ adj (defect$ or degeneration$)).ab,ti,ot.
24. or/9-23

IV. Diabetes mellitus:

25. exp diabetes mellitus/
26. diabet$.ab,ti,ot.
27. IDDM.ab,ti,ot.
28. NIDDM.ab,ti,ot.
29. MODY.ab,ti,ot.
30. (maturity onset adj diabet$).ab,ti,ot.
31. hyperinsulin$.ab,ti,ot.
32. insulin sensitiv$.ab,ti,ot.
33. insulin$ resist$.ab,ti,ot.
34. (non insulin$ depend$ or noninsulin$ depend$ or non insulin?depend$ or noninsulin?depend$).ab,ti,ot.
35. ((typ$ 1 or typ$ 2) and diabet$).ab,ti,ot.
36. ((typ$ I or typ$ II) and diabet$).ab,ti,ot.
37. exp Insulin Resistance/
38. (insulin$ depend$ or insulin?depend$).ab,ti,ot.
39. or/25-38

V. Eye diseases + Diabetes mellitus

40. 24 and 39

VI. II + V:

41. 8 or 40

VII. RCT/CCT (sensitive search):

Part 1:

42. randomized controlled trial.pt.
43. controlled clinical trial.pt.
44. randomized controlled trials.sh.
45. random allocation.sh.
46. double-blind method.sh.
47. single-blind method.sh.
48. or/42-47

(Continued)

Part 2:

49. clinical trial.pt.
50. exp clinical trials/
51. (clinic$ adj25 trial$).ab,ti,ot.
52. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).ab,ti,ot.
53. placebos.sh.
54. placebo$.ab,ti,ot.
55. random$.ab,ti,ot.
56. research design.sh.
57. (latin adj square).ab,ti,ot.
58. or/49-57

Part 3:

59. comparative study.pt.
60. exp evaluation studies/
61. follow-up studies.sh.
62. prospective studies.sh.
63. (control$ or prospectiv$ or volunteer$).ab,ti,ot.
64. cross-over studies.sh.
65. or/59-64
66. 48 or 58 or 65

VIII. Pentoxifylline + Diabetic retinopathy + RCT/CCT

67. 7 and 41 and 66

IX. Meta-analysis:

68. exp meta-analysis/
69. exp Review Literature/
70. meta-analysis.pt.
71. review.pt.
72. or/68-71
73. letter.pt.
74. comment.pt.
75. editorial.pt.
76. historical-article.pt.
77. or/73-76

78. 72 not 77

79. ((systematic$ or quantitativ$ or methodologic$) adj (review$ or overview$)).ab,ti,ot.
80. meta?anal$.ab,ti,ot.
81. (integrativ$ research review$ or research integration$).ab,ti,ot.
82. quantitativ$ synthes$.ab,ti,ot.
83. (pooling$ or pooled analys$ or mantel$ haenszel$).ab,ti,ot.
84. (peto$ or der?simonian$ or fixed effect$ or random effect$).ab,ti,ot.
85. or/79-84

86. 78 or 85

X: Pentoxifylline + Diabetic retinopathy + Meta-analysis
87. 7 and 41 and 86

XI. VIII + X:

88. 67 or 87

(Continued)

89. limit 88 to animal
90. limit 88 to human
91. 89 not 90
92. 88 not 91

WHAT'S NEW

Date	Event	Description
24 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

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Organizing retrieval of papers: CCLJ, OV
Screening retrieved papers against inclusion criteria: CCLJ, OV.
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Providing additional data about papers: CCLJ.
Obtaining and screening data on unpublished studies: CCLJ, OV.
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Analysis of data: CCLJ, OV, VFMT
Interpretation of data: CCLJ, OV, VFMT.
Writing the review: CCLJ
Performing previous work that was the foundation of the present study: CCLJ
Guarantor for the review (one author): VFMT
Statistical analysis: OV, VFMT.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Diabetic Retinopathy [*drug therapy]; Pentoxifylline [*therapeutic use]; Vasodilator Agents [*therapeutic use]

MeSH check words

Humans